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### ADDRESS OF THE PRESIDENT

#### THE CRITICAL LATENT OR LAG PERIOD IN THE HEALING OF WOUNDS\*

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THIS GREAT HONOR of election to the presidency of the American Surgical Association is deeply appreciated, especially when I consider the character and ability of my predecessors and the standing and attainment of you, my colleagues, who have conferred upon me this durable distinction.

It seems strange that in the more than half century of the life of this Association, 50 years of the greatest advances in the history of surgery, none of the Presidential Addresses have dealt with the subject of wound healing. Was it because it was considered an old, commonplace subject of insufficient interest to surgeons? Rather, I believe, it was because the subject presented many poorly understood biologic factors and controversial points of technic which made those, who had been chosen by their associates to preside over their meetings, hesitate to present such an everyday topic. This makes my temerity the greater in attempting to present a certain phase of the subject before such an experienced and critical group of surgeons.

I have chosen this topic—the lag period or phase of adjustment in wound healing—because it is the critical period of repair in which is initiated the sequence of definite processes leading to the fibroplastic fusion of the wound surfaces, and because this sequence may be helped or hindered by the surgeon in his management of the patient and of the wound.

\* Delivered before the American Surgical Association, May 1, 1940, St. Louis, Mo.

Wound repair is preeminently a surgical problem. As surgeons, we treat accidental wounds—and we make wounds. We should, therefore, be particularly interested in their optimum repair and the part we may take in accelerating or retarding the reparative process. As teachers in medical schools, and as senior surgeons in leading hospitals, our example and our interest in wound repair play a major part in the sound basic training and apprenticeship of the younger attending surgeons and residents who will follow us in handing on the fine traditions of American surgery.

Wound healing is a composite biologic phenomenon which conforms, in general, to the laws of growth. The processes involved interact with one another, but each shows quantitative variations, depending upon the tissue involved in relation to the conditions present in the wound. The three most important processes involved in wound repair are: (1) The ameboid movement; (2) the mitotic proliferation; and (3) the maturation of the cells engaged in the fusion of the wound surfaces. But before ameboid movement and mitotic proliferation can progress, certain activities in the wound space and the bordering tissues of the wound surfaces must first be completed. These activities take place during the latent or lag period. Their extent and relative interaction are determined by both local and systemic conditions.

The local factors are: (1) The amount of killed or damaged tissue in the wound surfaces; (2) the vascularity of the tissues involved. The more abundant the capillary bed the more rapid the repair; (3) the integrity of the blood flow to the damaged tissue. This determines the nutrition and viability or the necrosis of the tissues bordering on the wound surfaces; (4) the amount and character of the exudate in the wound space and in the tissues bordering the wound; (5) the number and character of infectious organisms in the wound space and the bordering tissues; (6) the number and character of foreign bodies to be extruded or encapsulated.

The systemic conditions which determine the duration of the lag period and which have a profound influence on one or more of the local factors are: (1) The age of the tissues, whether they are adolescent, normal adult or senescent and degenerated; (2) the state of normal hydration. Dehydration or overhydration of the tissues is determined by the water, electrolyte and protein balance in the blood, and may profoundly alter the conditions in the wound surfaces and the wound space contents; (3) normal nutritional balance. Protein deficiency retards, high protein diet accelerates wound healing. Fat heals slowly. A high fat diet prolongs the repair of wounds; (4) vitamin balance. It has been definitely shown that both C avitaminosis and C vitamin deficiency prolong the lag period because of the essential rôle of vitamin C in the formation of intercellular substance and the maturation of the fibroblast and the transformation of fibrous to collagen fibers; (5) the state of the general circulation and blood picture. Poor circulation and severe anemia definitely alter or delay wound healing.

In the study of wound healing the least complicated sequence of reparative processes is seen in the cleanly incised wound made and closed with



the strictest aseptic, atraumatic and hemostatic technic. For this reason such a wound is of the greatest interest to both biologist and surgeon. In such a wound the lag period of four days is uniform provided there are none of the systemic deleterious factors present. The initial escape of blood and plasma is minimal, the formation of a fibrin mesh from the plasma is not unduly delayed by the necessity of elimination of much dead tissue by autolysis, heterolysis, and phagocytosis, and the excessive exudate of bacterial and foreign body reaction does not widely separate the wound surfaces. The quiescent period of agglutination of wound surfaces by a thin layer of fibrin in such a wound is short.

Whether there is a definite initiation of the ameboid movement of new connective tissue cells by growth stimulating substance elaborated by freshly damaged cells is not yet proven. Some 20 such activating factors have been described. Certainly, in tissue cultures it has been shown by Carrel and his associates<sup>1</sup> that embryonic tissue juice stimulates cell growth. Products of cell destruction are considered by many workers to have a stimulating effect on the reparative process. Baker<sup>2</sup> considers glutathione and hemoglobin to be the stimulating substances in fibroblastic proliferation. Hammett<sup>3</sup> claims the sulphhydryl radical as the essential effective stimulus to cell proliferation in wound repair. Von Gaza<sup>4</sup> believes that the inadequacy of oxygen supply and other nutritive substances in the ischemic border or plane in wounds leads to a tissue hunger which initiates cell division and ameboid activity of fibroblasts and endothelial buds.

The destructive or lytic phase by which dead tissue is removed is succeeded by ameboid movement into the fibrinous zone of fibroblasts, derived not from the adjacent fixed tissues but from the wandering connective tissue cells, fibroblasts, polyblasts and histocytes. At this time mitotic proliferation of these mesenchymal connective tissue cells is accelerated.

Leo Loeb<sup>5</sup> has emphasized the importance of two processes in this stage of the lag period connected with the ameboid movement and proliferation of the invading fibroblasts. The first is the phenomenon of stereotropic response of growing cells to surfaces. Fibroblasts in contact with fibrin strands or fibrils have a strong tendency to elongate and grow along the fibrils, just as epithelial cells show ameboid movement along plane surfaces of granulation tissue or beneath the scab. The second reaction is a centrifugal force which directs the cells away from their own tissue and into the plasma mass in the wound space. This induces various kinds of cells, including fibroblasts, to move into blood clot in a fan-like manner to take part in the organization of the clot. Similarly, endothelial buds show a centrifugal growth into the organizing fibrin with a spread of the vascular bed and thus enter into the formation of granulation tissue.

These reactions may be considered essentially the reactions of cells to foreign bodies. Surface changes in cells lead to agglutination and occur in response to the stimuli which may well be due to differences in electric poten-

tial. Ameboid movements, phagocytosis and giant cell formation represent different manifestations and degrees of the same reactions.

With the maturation of the fibroblasts and their elongation along the fibrin fibrils uniting the wound surfaces, and the development of collagen fibers from the elongated fibroblasts, there takes place the change from the lag period of no appreciable tensile strength in the wound to the second phase of wound healing, the period of fibroplasia, characterized by a sudden and rapid increase in tensile strength. Harvey and Howes,<sup>6</sup> in their many contributions to the study of the tensile strength of wound repair, have established wound healing on a firm physiologic basis and have given surgery the soundest and the simplest rationale for the management and technic of wound repair. For the tensile strength of the wound is what really matters, both in the rapidity and permanency of its accomplishment.

From the practical surgical standpoint the lag period is the interval between the receipt of the wound and the beginning of tensile strength, during which time the wound surfaces have to be held together by mechanical means, by sutures, by splinting, or by constantly maintained pressure. These measures must be carried out with the least damage to the wound surfaces and bordering tissues, maintenance of maximum nutrition, adequate blood supply, minimum foreign body reaction, and maintenance of rest by immobilization of the damaged tissues. This is the period of wound repair where the surgeon can contribute constructively or destructively by the intelligent employment of his art.

It is in his efforts to insure and maintain wound repair that the thoughtless surgeon makes his most common mistake by suturing the wound edges and individual layers too tightly—and with suture material out of all proportion to the holding strength of the tissues. Anyone who has studied the vascular bed of the peritoneum or of muscle by micromanipulation technic is aware of the minute amount of pressure necessary to obstruct or obliterate the blood flow in the capillaries and the arteriovenous channels. Undue tension in the sutures will cause wide zones of anemic, even ischemic tissue, thus prolonging the lag period, by increasing the lytic process in the wound.

In no field of surgery is this factor of tension ischemia better illustrated than in intestinal anastomosis. Fortunately the peritoneal layer, because of its very rich capillary bed, is the surgeons', as well as the patients', best friend. The recent introduction of the Miller-Abbott tube as a preoperative measure in resections of the small intestine and in right-sided colectomies, has reduced the mortality following these major procedures 50 per cent—all due to the fact that the bowel is deflated before and after the anastomosis, thus removing that ominous factor of tension.

It is in the understanding of the systemic factors of wound healing that the most recent advances have been made. In this field the science of surgery adds immeasurably to the art of wound repair. Attention is called to these factors outside of the wound in the management of repair.

(1) *Age Influence*.—Clinically, it has always been known that wounds

heal more rapidly and firmly in the young than in the old. DuNoüy<sup>7</sup> demonstrated a faster rate of wound healing in young animals, and Howes and Harvey<sup>8</sup> found in young rats an earlier onset of fibroplasia, a lessened retardation, and an earlier termination of the process. It becomes the more important to maintain tissue nutrition and avoid the local deleterious factors of infection and foreign body reaction in repairing wounds in the old patient and in senescent, poorly nourished tissue.

(2) *Normal Fluid Electrolyte and Protein Balance.*—The symposium that is to follow this address is evidence of the interest of the surgeon of to-day in this exceedingly important factor in tissue metabolism and tissue repair. Overhydration may cause as serious disturbance in wound healing and prolongation of the lag period as dehydration, for edema definitely delays the onset of fibroplasia. Extreme degrees of dehydration, as seen in prolonged or severe fluid and electrolyte loss, deplete intercellular fluid and may disturb the intracellular salt and fluid balance, which will threaten not only local wound healing but the individual himself. Methods, now perfected, for determining fluid and salt balance are essential in following the course of patients operated upon after, or with severe fluid loss from hemorrhage, fistulae or prolonged increased temperature. These same determinations of hematocrit and plasma specific gravity and acid-base ratio should be determined in order to avoid overhydration.

Protein deficiency, seen in hypoproteinemia, may be caused by prolonged protein starvation, or protein loss following hemorrhage, inflammatory exudate or fistula drainage. Hypoproteinemia, because of the reduced large molecular content of the blood, results in fluid loss from the capillary bed into the intercellular spaces and intercellular edema. Ravdin<sup>9</sup> and his associates have demonstrated abdominal wound disruption in over 70 per cent of dogs operated upon in the presence of hypoproteinemia. The wound edges in periods after wound closure were soggy with edema and, in some instances, showed no evidence of fibroplasia at the seventh and fourteenth days. The wound surfaces were held together only by the silk sutures employed in the closure. In wounds sutured with catgut only the knots were left; in others no remnants of catgut could be found. Unfortunately, we have all noted this same picture in disrupted abdominal wounds in depleted patients. It is essential to determine the blood protein level in the cachectic or depleted individual before operation and to precede surgery with measures directed toward raising the protein content to normal. Plasma transfusions and, whenever possible, because more effective, the Miller-Abbott tube should be employed for administering split-protein products which the patient cannot take by mouth.

(3) *Normal Nutritional Balance.*—Protein maintenance, aside from its effect on intercellular fluid, is necessary to provide cellular nutrition. The manner in which tissues obtain their nitrogen and build up their new protoplasm still remains a mystery, but the fact is that tissues in the wound require protein as well as the tissues elsewhere. Clark<sup>10</sup> was the first to study the

effect of diet on the healing wound. It is interesting that the type of diet employed influenced the total period of healing proportionately as it affected the latent period—a high protein diet eliminated the lag period, whereas a high fat diet prolonged it to six days.

Herrmannsdorfer<sup>11</sup> claimed that an acid diet exerted a marked effect in hastening wound healing, on the ground that bacterial growth is inhibited; whereas on an alkaline diet the wound swarmed with bacteria, and was accompanied with a foul exudate. Reimers and Winkler<sup>12</sup> produced an acidosis in dogs, through the administration of ammonium chloride, and found a definite shortening of the period of wound healing.

(4) *Vitamin Balance*.—Of the enormous amount of research undertaken to establish the rôle of the many vitamins in tissue metabolism, two vitamins have emerged as being of special significance in relation to wound healing.

*Vitamin C*.—It is now well-established that intercellular substance in general, and especially in the capillary bed, and the collagen of all fibrous tissue require ascorbic acid for their production and maintenance. Höjer<sup>13</sup> found an atrophy of connective tissue in scorbutic guinea-pigs, and was the first to call attention to a general deficiency in collagen formation. Wolbach,<sup>14</sup> in this country, has confirmed these findings and has shown that ascorbic acid is intimately concerned with the synthesis and maintenance of intercellular supporting substance. This is of special significance in the capillary bed where lack of or deficient intercellular cement substance results in hemorrhage into the wound space and in the bordering tissues prolonging the lag period. Lanman and Ingalls,<sup>15</sup> and Taffel and Harvey<sup>16</sup> have shown by animal experiments that not only C avitaminosis but partial vitamin C deficiency causes a prolongation of the lag period and delays the return of tensile strength because of insufficient collagen fiber formation.

Methods of determining vitamin C in the blood are still inaccurate and are being refined. This accounts for the conflicting reports by workers in this field. There is still some uncertainty as to the length of time man can remain C-vitamin depleted before showing signs of scurvy, but the rôle of vitamin C in the formation of intercellular substance and collagen seems definitely established.

It is the partially deficient vitamin C state that is seldom suspected or anticipated. Holman<sup>17</sup> found that 44 per cent of the "run of the mill" patients in the Stanford-Lane Surgical Clinic wards were deficient in vitamin C—and this in the land of the Sunkist orange. Of 34 patients admitted to a London hospital,<sup>18</sup> 14 showed evidence of vitamin C deficiency. All those above 70 years of age showed relative deficiency. It was also found that patients admitted for peptic ulcer therapy showed no vitamin C deficiency, but four days of a strict ulcer dietary regimen resulted in a deficiency of vitamin C. This is a most important consideration in the preparation of patients, with ulcer or carcinoma, who have been on rigid diets, such as the Sippy regimen. They should regularly be tested for blood vitamin C content and not operated upon until the deficiency is corrected.



*Vitamin K.*—This more recently studied vitamin has a very essential rôle in the control of hemorrhage in relation to prothrombin deficiency. Of special significance, and life-saving, is the employment of vitamin K with bile salts in jaundiced or acholic patients. This is so well-known now that it is generally administered in all clinics. Jaundice is the warning signal to the surgeon for vitamin K therapy.

(5) *Circulatory Imbalance and Anemia.*—With present day methods for determining cardiac output and myocardial efficiency, the cardiovascular competence can be definitely determined before operation, and with direct donor transfusion or bank blood transfusion there is no excuse for operating upon markedly anemic patients. Hematocrit and blood plasma determinations have added tremendously to the scientific care of anemic and depleted patients before, during, and after operation.

The lag period is universal as a growth phenomenon. It is seen in plant, fungous and bacterial growth, as well as in the growth of cells in the repair of wounds. Because it is the interval during which the wound surfaces are held together by measures other than the natural body tissues and provided by surgical technics, this period is the surgeon's concern. Another most important rôle of the surgeon is in keeping the wound clean. When infection gains a footing the destructive stage of the lag period is prolonged or made to recur, with a corresponding delay in the fibroplastic phase. The destructive phase of the lag period due to infection is the dangerous period. In the presence of certain bacteria, such as the *Beta* hemolytic streptococcus or the colon group, the newer sulphonamide group of chemotherapeutic drugs prevent or shorten wound infection before the limiting pyogenic membrane prevents the diffusion of the drug by the blood stream. Local application of the crystals of these drugs promises real results in the control of bacteria in areas walled-off by pyogenic membrane or fibrinopurulent adhesions. These drugs *per se* do not hasten but rather seem to delay normal primary wound healing according to Bricker and Graham.<sup>19</sup>

Every true surgeon cannot help being interested in wound healing. The problems presented in the repair and management of the wound call for all the science as well as the art of surgery, especially in relation to the critical lag period of wound healing. The art of surgery, based upon the necessity for preventing tissue damage and foreign body reaction, consists of the aseptic and hemastatic use of sharp knife dissection, delicate instruments and fine suture and ligature material that is not more than twice as strong as the holding tissues. We can do this much at least in not making the lag period the dangerous period in wound healing.

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A most comprehensive and discriminating review of the subject "Wound Healing," including a very comprehensive bibliography, has been written by Leslie B. Arey, which is to be found in *Physiol. Rev.*, **16**, 327-406, July, 1936.

# SYMPOSIUM ON FLUID AND ELECTROLYTE NEEDS OF THE SURGICAL PATIENT

Presented Before

## THE AMERICAN SURGICAL ASSOCIATION

St. Louis, Mo., May 1, 2, 3, 1940

### THE STRUCTURE OF THE BLOOD IN RELATION TO SURGICAL PROBLEMS ✓

JOHN P. PETERS, M.D., New Haven, Conn.

### THE PRESERVATION OF BLOOD

DAVID C. BULL, M.D., and CHARLES R. DREW, M.D., New York, N. Y.

### STUDIES OF BLOOD PRESERVATION: THE STABILITY OF PLASMA PROTEINS

JOHN SCUDDER, M.D., New York, N. Y.

### SODIUM CHLORIDE METABOLISM OF SURGICAL PATIENTS ✓

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### FLUID, SALT AND NUTRITIONAL BALANCE IN PATIENTS WITH INTESTINAL SUCTION DRAINAGE ✓

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### A CLINICAL STUDY OF THE PLASMA VOLUME IN ACUTE INTESTINAL OBSTRUCTION

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### PLASMA LOSS IN SEVERE DEHYDRATION, SHOCK AND OTHER CONDITIONS AS AFFECTED BY THERAPY

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### PARENTERAL REPLACEMENT OF PROTEIN WITH THE AMINO-ACIDS OF HYDROLYZED CASEIN

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### THE RELATION OF PROPER PREPARATION OF SOLUTIONS FOR INTRAVENOUS THERAPY TO ALLERGIC AND FEVER REACTIONS

CARL W. WALTER, M.D., Boston, Mass.

Discussions by

DALLAS B. PHEMISTER, M.D.

J. SHELTON HORSLEY, M.D.

DAMON B. PFEIFFER, M.D.

WALTER E. LEE, M.D.

WILLIAM DEW. ANDRUS, M.D.

## THE STRUCTURE OF THE BLOOD IN RELATION TO SURGICAL PROBLEMS\*

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I HAVE CHOSEN to discuss some features of the treatment of gastro-intestinal disorders because these present, in the most exaggerated forms, the chief problem of fluid regulation. Before proceeding to particulars, however, I should like to touch upon certain general principles: First, it is reasonable to assume that reparative processes will be favored by measures that will preserve the integrity of both volume and composition of the body fluids.

All the secretions of the gastro-intestinal tract are approximately isotonic with blood serum, that is, they contain approximately equal concentrations of chemical components. Furthermore, in all these secretions, as in the serum, sodium salts predominate. The chief acids in these fluids are chloride and bicarbonate, chloride giving way more and more to bicarbonate in the descent through the alimentary canal. These facts are illustrated in Figure 1. It follows that a liter of gastro-intestinal contents is roughly equivalent, as far as sodium is concerned, to a liter of normal saline. (An exception must be made of acid gastric contents, in which the sodium is partly replaced by the hydrogen ion.) On the whole, it may be roughly stated that secretions lost from the alimentary canal will contain, on the average, about 0.5 to 0.6 per cent of chloride, estimated as sodium chloride.

Fluids introduced into the stomach or intestine rapidly assume a composition which resembles, so far as salts are concerned, that of the native secretions of these viscera. For example, when water enters the stomach or intestine, enough salt is poured into it to make it isotonic with the blood serum and the composition of the salt mixture assumes the electrolyte pattern characteristic of that portion of the alimentary canal in which it happens to be. If, therefore, a liter of water or saltless fluid, introduced into the intestine, is lost by vomiting or through a fistula, it will remove with it approximately the salt from one liter of serum or interstitial fluid. Under these circumstances the salt concentration—and consequently the osmotic pressure—of the body fluids will fall. Within limits, the body reacts on behalf of osmotic pressure by excreting an equivalent amount of water through the kidneys. The administration of water by mouth, under these circumstances, becomes, paradoxically, a dehydrating measure.

The sequence of events can be illustrated by the example of pyloric stenosis, represented diagrammatically in Figure 2. A depicts the pattern of normal serum. The vertical dimension of each column represents the concentration of bases or acids in the serum, while the horizontal dimension represents the volume of fluid within the body in which these are dissolved.

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\* Read before the American Surgical Association, May 1, 2, 3, 1940, at St. Louis, Mo.

# BLOOD IN RELATION TO SURGERY

The figures at the bottom indicate what proportion of the components indicated still remains in the body at each interval. For instance, at C 90 per cent

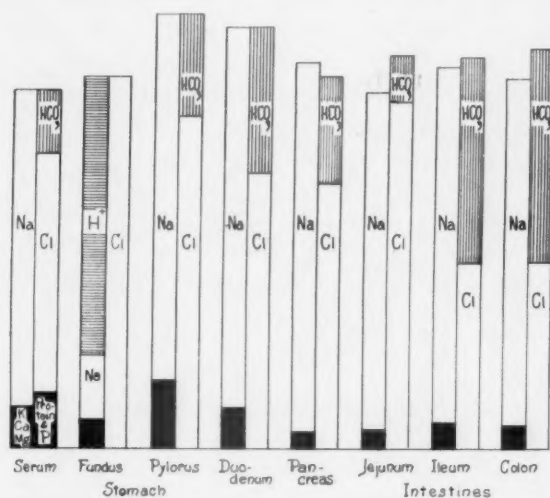


FIG. 1.—The concentration of bases (cations) and acids (anions) in the serum and gastro-intestinal secretions. (Compiled from the literature)

of the original body water remains, or 10 per cent has been lost. The first event is the loss of chloride as hydrochloric acid in the vomitus, represented

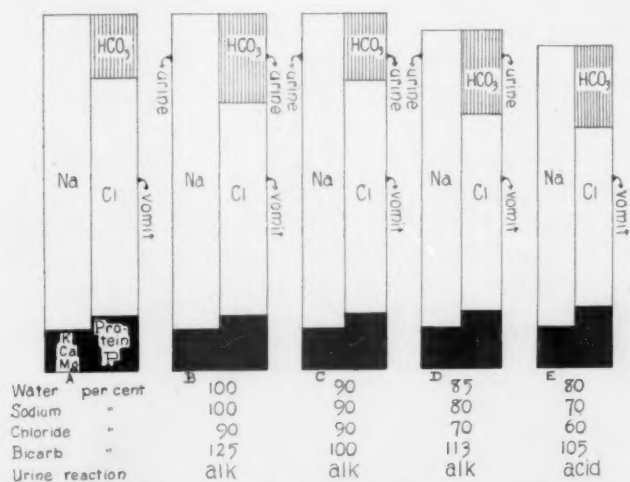


FIG. 2.—Progressive changes in the chemical pattern of the serum in the vomiting of pyloric obstruction. The vertical dimensions of the columns represent concentrations of electrolytes, the horizontal dimensions volumes of fluid in the body. The figures below the chart indicate the quantities of various components remaining in the body at each stage of the progression, in per cent of the quantities originally present.

by the curved arrow on the right of A. The sodium formerly combined with the chloride is left behind to form bicarbonate with  $\text{CO}_2$ . The result is bicar-

bonate excess or alkalosis, represented in B. At this stage, in order to restore a normal serum pattern, excretion of chloride into the urine ceases; the kidney excretes an alkaline urine containing sodium bicarbonate. This mitigates or abolishes the bicarbonate excess. Meanwhile the fluid content of the body has also been reduced. The net effect, pictured in C, is the restoration of the normal composition of the body fluids at the expense of volume (represented by the narrowed columns). Although 10 per cent of the chloride and 10 per cent of sodium have been lost, because of the coincident discharge of 10 per cent of water the pattern appears almost normal. As the vomiting continues, water being taken throughout, a point is reached at which fluid can no longer be spared. The sodium concentration falls, as D shows, since bicarbonate is still sacrificed in the urine in behalf of the acid-base equilibrium to balance chloride lost in the vomitus. If the vomiting proceeds a little further a most anomalous condition ensues. Despite increasing bicarbonate excess the urine suddenly becomes acid. A state has now been reached, illustrated in E, in which no further loss of sodium is tolerated. Acid-base equilibrium is forced to yield to the demands of osmotic equilibrium. In this final stage dehydration, alkalosis, salt depletion and reduction of osmotic pressure are all combined.

A similar series of figures could be drawn to illustrate the course of events in severe diarrhea. In this condition bicarbonate is lost in the stools, while chloride is excreted in the urine. The end-result is a deficiency of sodium and bicarbonate with a relative excess of chloride in the depleted body fluids.

The concentrations of sodium, bicarbonate and chloride in the serum give valuable information concerning the severity of vomiting and diarrhea and the extent of the consequent depletion of salt and water. They also provide a check upon the efficacy of therapeutic measures—aimed to overcome these defects. Determination of sodium is too difficult and time consuming for clinical purposes. Since, however, as the figure shows, the sodium salts of serum consist almost entirely of bicarbonate and chloride, its concentration may be estimated with sufficient accuracy from the sum of the concentrations of bicarbonate and chloride.

There is reason to believe that body cells swell when the salt concentration in the body fluids falls, just as red blood cells swell in hypotonic salt solution. Such swelling must seriously impair functional integrity. The most obvious clinical effects of salt depletion and dehydration are shock and failure of renal function, the latter manifesting itself in elevation of the blood non-protein nitrogen. Subcutaneous or intravenous normal saline usually rectifies the disorder, although hypertonic salt is to be preferred when salt depletion is profound. If enough is given to restore the volume of the body fluids and to establish an adequate flow of urine the kidneys will adjust the composition of the body fluids quite readily.

These physiologic facts seem to have certain inescapable implications: First, the alimentary canal is not relieved of work by the introduction of



fluid, and especially water. Second, efforts should be directed to prevention of distention rather than to decompression of stomach or intestines. Third, if only physiologic isotonic solutions are introduced into the alimentary canal, dehydration and salt depletion will be minimized and the need for parenteral fluids will be proportionally diminished.

The best way to rest the alimentary canal is to give it nothing to do. Foster<sup>1</sup> and others have shown that if no water or food is given to dogs after ligation of the pylorus, vomiting ceases after a short interval. If only enough saline is given parenterally to replace the fluid and salt lost in the initial vomitus these dogs live just as long as unoperated dogs deprived of food and water. Is there any reason to believe that humans would not behave like these dogs if they were given a chance? In mercury poisoning, although the whole gastro-intestinal tract is ulcerated and irritated to an extreme degree, complete withdrawal of fluids and food by mouth is succeeded almost immediately by cessation of both vomiting and diarrhea.<sup>2</sup> The term "complete" permits no compromises nor exceptions, not even water in sips or cracked ice.

#### ILLUSTRATIVE CASE REPORTS

**Case 1.**—No. A-1066: A male, age 14, on September 5, had a brain abscess drained. After operation he was treated with sulfapyridine, and was given as much cracked ice as he desired. He vomited with steadily increasing frequency. After three days, although he had received, by infusion and hypodermoclysis, 7,500 cc. of fluid containing 300 Gm. of glucose and 20 Gm. of sodium chloride, he presented the condition pictured in the second column of Figure 3 (the first column represents the pattern of normal serum); namely, completely anuric, pulse 130, blood nonprotein nitrogen 90 mg. per cent, serum proteins 9.3 per cent denoting extreme hemoconcentration. Serum chloride was reduced to 69 mg. per cent (30 per cent below normal); bicarbonate was approximately normal. All food and fluids, including ice, by mouth, were stopped and he was given parenterally 6,500 cc. of water containing 125 Gm. of glucose and 64 Gm. of salt. Vomiting and hiccough ceased at once. Within 24 hours the pulse had fallen to a normal rate, the nonprotein nitrogen had dropped to 46 mg. per cent and he was voiding freely. Serum chloride and bicarbonate had been restored. At the end of three days, during which he vomited only 10 cc., the nonprotein nitrogen was normal (28 mg. per cent), and the serum proteins had fallen to 6.8 per cent. A liquid diet was given that day and on the next he was able to take a soft diet.

**Case 2.**—No. A-60808: A male, age 43, because of hemorrhages, and slow perforation of a gastric ulcer, was subjected to plication of the ulcer and gastro-enterostomy. Two years later, after two weeks of increasing pain and vomiting, culminating in hemorrhage, he was readmitted to the hospital with signs indicative of slow perforation again.

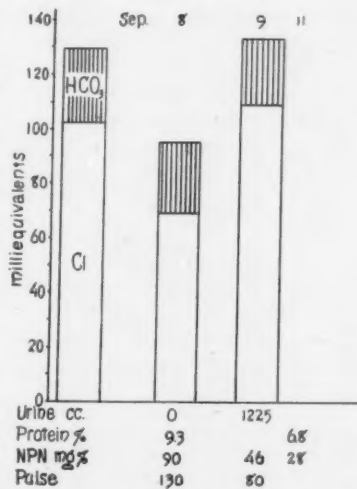


FIG. 3.—Case 1, No. A-1066: The concentrations of bicarbonate and chloride in the serum. The column on the left shows the pattern of normal serum. The figures at the bottom give urine volume, blood nonprotein nitrogen, serum protein and pulse rate.

With nothing by mouth, he vomited only 20 cc. in four days, but vomited increasingly when a Sippy dietary regimen was given for three days. When everything was withheld again by mouth he vomited only 30 cc. in three days; but once more vomiting returned when he resumed fluids. In each instance, with the cessation of vomiting, other symptoms disappeared. Dehydration was relieved and thirst allayed by parenteral administration of moderate amounts of fluid containing salt. (Needless to say, operation was resorted to when conservative treatment proved ineffective.)

It has been possible, in a few cases, to prove that the vomiting resulting from pyloric obstruction will respond to withdrawal of food and fluids. It may be necessary for the first day or two to empty the stomach if it becomes distended; but there is no apparent advantage in lavaging the stomach, nor in leaving in the stomach a tube or fluid to stimulate secretion. Before any such procedures are instituted the more physiologic process of rest should be given a reasonable trial.

If inlying tubes are used, however, to relieve distention, any fluid introduced into the alimentary canal through them should contain enough salt to make it isotonic with blood serum, especially if the stomach or intestine is obstructed or contains a fistulous opening. To give water by mouth or tube, and saline parenterally, is not equally satisfying. It is next to impossible to establish salt and water equilibrium or a positive balance by this method, even if it were not unduly distressing to the patient. The introduction of water into the obstructed bowel or stomach seems to provoke the excretion of further fluid as well as salt.

**Case 3.**—No. A-25125: A female, age 43, who had previously undergone a pelvic operation, entered the hospital with symptoms and signs of intestinal obstruction of four days' duration. Her fluid and salt balance are roughly presented in Table I. Fluids were measured. The salt intake is known. On the basis of other studies, it is estimated that the drainage from the stomach contained chloride equivalent to 0.6 per cent of sodium chloride, while the urine contained no chloride. The chloride excretion is, therefore, probably underestimated. A Wangenstein tube was introduced, and for two days only, small amounts of saline were administered. During the same period 5,500 cc. of water containing 27 Gm. of salt were administered parenterally. Drainage

TABLE I

Day	Water Intake				Water Out			NaCl			
	Wangen- steen Cc.	Oral Cc.	Paren- teral Cc.	Total Cc.	Drain- age Cc.	Urine Cc.	Total Cc.	Water Bal- ance Cc.	In Gm.	Out Gm.	Bal- ance Gm.
1	2,100		3,500	5,600	2,100	1,300	3,400	2,200	28	13	15
2	2,350		2,000	4,350	3,300	1,200	4,500	-150	30	20	10
3	1,900	3,400	0	5,300	9,500	550+	10,050	-4,750	17	57	-40
4	2,050	4,350	1,500	7,850	11,200	500	11,700	-3,850	27	67	-40
5	2,100	3,200	3,000	8,300	5,700	1,100	6,800	1,500	37	34	3
6	3,200	1,500	6,500	11,200	8,800	2,300	11,300	100	83	53	30
7	2,250	0	3,000	5,250	2,700	1,450	4,150	1,100	47	16	31
8	1,750	Cracked ice	3,000	4,750+	1,800	1,300	3,100	2,650	43	11	32

through the Wangenstein only slightly exceeded the fluid introduced through the tube. Positive water and salt balances were established; dehydration was alleviated; and urine volume was adequate. The condition seemed so favorable that on the third day parenteral fluids were omitted while nutrient fluids without salt were given by mouth. Although only 3,400 cc. of salt free fluid were given this way, drainage from the Wangenstein increased from 3,300 to 9,500 cc.—i.e., by 6,200 cc. There was a negative water balance of almost five liters, and an estimated salt deficit of 40 Gm. The urine volume fell sharply. The next day drainage rose to 11 liters. The following day, by the administration of 3,000 cc. of saline parenterally, the urine volume rose to one liter, and slight positive balances of water and salt were established. At the end of the five days, serum chloride was only 78 m.eq. (25 per cent below normal; bicarbonate was 37 m.eq.), 10 m.eq. above normal. There was a total salt deficit with alkalosis. The blood non-protein nitrogen was 45 mg. per cent (distinctly elevated); the serum proteins were 7.2 per cent (evidence of dehydration in one who was undernourished).

On the following day, by the parenteral injection of an enormous amount of saline (6.5 liters), it was possible to turn the tide. The balance of water was barely positive, if insensible perspiration be ignored. But at what expense! All the fluids that entered the mouth, and most of that given by vein or under the skin, were recovered in the Wangenstein drainage. Contrast this with the next two days. When saltless fluids by mouth were again withdrawn, the drainage diminished at once by 6,100 cc., although the fluid given by mouth and tube was reduced only 2,500 cc. The next day she received only a little cracked ice by mouth. Drainage remained small. At the end of this period the general condition of the patient was greatly improved; urine flow was adequate; blood nonprotein nitrogen normal (26 per cent); the serum proteins had fallen to 6.7 per cent. Serum bicarbonate was normal, chloride distinctly elevated (to 115 m.eq.). This hyperchloremia must not be regarded as a sign that too much chloride has been given, but rather that dehydration has not been entirely overcome. The patient had probably stored little water, if account is taken of the insensible perspiration, but she had retained large quantities of salt. I may add that the intestinal obstruction was overcome without operative intervention.

Table II summarizes the published data<sup>3</sup> from a patient with obstruction of the ileum who was decompressed and fed by means of the Abbott-Miller double tube. The authors imply that loss of water and electrolytes was prevented. In actual point of fact, the positive water balance for the four-day period was not more than large enough to provide for the losses that must have been incurred through the urine and insensible perspiration. The drainage from the tube far exceeded the fluid introduced through the tube and washed out all the salt which was given by vein. Less water and salt might have been lost in the drainage if the fluid given by mouth had contained salt. The procedure was particularly unphysiologic in this case, since Dennis<sup>4</sup> has shown that water has a peculiarly injurious effect upon the mucosa of the ileum.

The following case illustrates a somewhat different phase of the same problem.

**Case 4.**—No. A-75015: A female, age 19, with ulcerative colitis and polyposis of the colon, was admitted with a recurrent perirectal abscess and fecal fistula which necessitated an ileostomy. She was greatly emaciated, weighing less than 80 lbs. All attempts to improve her condition were unavailing because of the amounts of food and fluid which

TABLE II

## FOUR DAYS' INTESTINAL OBSTRUCTION

(Abbott and Miller)<sup>2</sup>

## Fluid in:

By mouth.....	19,525 cc.	
By vein.....	10,930 "	
Total.....	30,455 "	
Drainage.....	23,400 "	
Balance.....	7,055 "	
Balance per day .		1,764 cc.

## Salt (as NaCl) in:

By mouth.....	9.7 Gm.	
By vein.....	106.9 "	
Total.....	116.6 "	
Drainage.....	111.1 "	
Balance.....	5.5 "	
Balance per day .		1.4 Gm.

escaped through the ileostomy. Moreover, salt depletion could only be prevented by frequent parenteral injection of saline. Finally, without changing her diet, which consisted of high caloric low residue foods, she was given in addition enough 1 to 3 per cent sodium chloride solution to drink to make all the food and fluids which she took isotonic with the blood serum. Within three days the discharge from the ileostomy, which had varied from 1,000 to 1,500 cc. daily, fell to from 400 to 800 cc. At the same time serum chloride and bicarbonate became normal. By the end of seven months she weighed 120 lbs., a gain of 40 lbs. There has not yet been an opportunity to repeat this procedure to learn whether it will succeed in other patients with intestinal fistulae. But it seems logical that by making the nutritive fluids which enter an irritable or irritated intestine isotonic with serum by means of sodium chloride, hypersecretion and hyperactivity may be reduced and absorption promoted.

## CONCLUSION

Distention and vomiting, either before or after operation, may often be allayed or checked by resting the gastro-intestinal tract as completely as possible. Complete rest is most easily achieved by withholding all food and fluids by mouth. If drainage by tube or lavage is instituted because this course or the courage of the physician fails, care should be taken that as little fluid as possible is introduced and that all food or fluid given by mouth or through the tube contains enough salt to make it isotonic with blood serum. This allays secretory and motor activity of the gastro-intestinal tract and mitigates dehydration and salt depletion. If the sum of bicarbonate plus chloride in the serum is reduced, saline should be administered parenterally to restore the fluid and salt content of the body. Glucose may be added to the intravenous saline to provide some nutrition and to reduce protein metabolism. It is unnecessary, however, under these circumstances, to administer large amounts

of fluid parenterally. Only enough is required to establish an adequate volume of urine. The patient who is excreting 1,000 to 1,500 cc. of urine daily is seldom a subject for anxiety.

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## THE PRESERVATION OF BLOOD\*

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WHEN THE PRESBYTERIAN HOSPITAL was considering the establishment of a Blood Bank, there was a demand for data as to what might be expected of preserved blood. It was appreciated that while the ultimate verdict would come from the clinical experience of its use, something of its potential dangers and benefits could be learned by preliminary work in the laboratory. Studies were, therefore, undertaken to find out what changes take place in preserved blood and the best methods of preserving it. This communication will summarize some of the findings but will of necessity omit description of methods, calculations, and other details.

To follow the deterioration of the cells, complete blood counts were made daily on blood preserved in a refrigerator at 4° C., with heparin as the anticoagulant. A similar series was made on citrated blood. The red cell counts varied, of course, but their mean remained about the same for 30 days in the heparinized blood. In citrated blood there was little change during the first 15 days, then a slow loss of from one to one and one-half million cells by the end of the month. According to Ponder, this loss is unimportant from a functional standpoint, as the capacity of the stored blood to carry oxygen remains unimpaired. The hemoglobin level remained constant, although increasing amounts of it up to 25 per cent were to be found in the plasma.

The mean cell diameter of the red cells steadily decreases from a base value of 7.6 to 5.8 microns at 35 days. The late loss could be due to escape of hemoglobin but this cannot account for the shrinkage of the first week which must depend upon salt and water loss.

Philip Levine<sup>2</sup> has submitted some interesting data on the length of life of a transfused red cell in the recipient. Identifying the donor cells in the patient by means of the group specific factors M and N, he found that cells stored 3, 10, or 14 days survived for 80, 60, or 20 days, respectively, as compared with cells of fresh blood, which lived over 95 days.

Volume index also decreased progressively—partly, perhaps, from the disappearance of white blood cells but mostly from the shrinkage in size of red cells.

The white blood corpuscle total count fell 50 per cent during the first 24 hours, and by the sixteenth day the cells remained only as smudges or amorphous masses. Polymorphonuclear leukocytes changed earliest and disinte-

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grated most rapidly, but eosinophils and basophils were recognized distinctly as late as the thirty-fifth day.

The thrombocyte count fell rapidly to a low level, near which it remained for 15 days. The platelets of blood preserved in citrate solution had a slightly slower initial fall. Determinations of erythrocyte fragility gave poor end-points. It was clear, however, that cells on the tenth day were less resistant than on the first, and still less resistant on the thirtieth.

With these data in mind, it is apparent that the red cells of preserved blood can be depended upon to function satisfactorily. To transfuse stored blood for the sake of its white cells or platelets, however, would be a questionable procedure. If we think of the immune factors of blood as being associated with them, then the use of fresh blood for infection would be more logical.

The prothrombin percentage, as measured by the Quick method, after a prompt initial fall remains at 50 for a long period. In many cases this amount would be inadequate.

Of the several electrolytes of the blood, potassium is important as the chief mineral base of the red cells; in the serum, however, only one-twentieth of the amount in the cells is found. As has been observed before, plasma standing in contact with cells tends to be enriched with cell potassium. On measuring this diffusion process it was found that the rise of plasma potassium begins immediately the blood is withdrawn, continues at a rapid rate for the first few days, and then more slowly until equilibrium is established. This does not depend upon contamination.

Various preservatives modify the time at which hemolysis begins, and one (Peyton-Rous mixture) actually prevents it. But none of those recommended prevents potassium diffusion. The best record was made by a mixture of 0.3 Gm. of sodium citrate per 100 cc. The difference in rates at which cells lose potassium and hemoglobin shows that the latter is not a very sensitive criterion of cell deterioration. Nearly one-half the potassium had escaped from the cell before any of the larger hemoglobin molecules were lost. There is a real increase of plasma potassium as the result of shaking. In fresh blood this is not as pronounced as it is a few days later. Unavoidable transportation of preserved blood should be undertaken immediately rather than when it has become several days old.

While the material of the container was not proved to be of importance, the shape exerts a definite effect. Blood in an Erlenmeyer flask, for example, shows a more rapid rise in plasma potassium than blood in a test tube; in fact the rate of potassium diffusion varies as the diameter of the area where cells and plasma are in contact.

Investigation of placental blood by similar methods revealed that potassium leaves the cells at much the same rate. Another similarity was the superiority of an 0.31 per cent sodium citrate solution over the Russian citrate compound as a preservative. Judged by their rate of potassium loss, cells of placental blood deteriorate about as do adult cells.

Our interest in potassium was not purely as an index of loss of vitality of

red cells, but also for its possible toxicity. The intravenous minimum lethal dose of potassium for man is not known, and the acceptance of animal tolerance as a guarantee of safety is admittedly fallacious unless a comfortable margin of safety is provided. By analogy, then, three to five liters of blood with plasma containing 100 mg. per cent could cause the death of a healthy adult. However, animal tolerance for a potassium infusion is increased many times by administering it slowly. It is unlikely that so much blood would be infused except very slowly as a drip, and improbable that any harm would result.

In patients whose excretion is handicapped or whose serum potassium is already high, care in the use of aged blood is advisable. Particularly in hemorrhage and shock, where the tendency is to transfuse large amounts rapidly, one should use caution or fresh blood.

The higher values of plasma potassium in cadaver blood are striking. At the time of collection it is found at levels found in preserved blood on the fifth day. This could be due in part to the disease which produced death. Another factor is temperature. Diffusion of potassium is much more rapid at 38° than at 4° C., and a cadaver is not chilled as suddenly as is blood under the usual conditions of preservation. A further possibility is the formation of ammonia from breaking down of body proteins. Ammonia could increase cell permeability, as it does in certain plant cells.

Ammonia nitrogen is found in infinitesimal amounts in normal blood but rises rapidly in the first few minutes of exposure to air. It continues its marked rise for four days, to reach the level of 1 mg. per cent, where it remains until the tenth day.

The direction taken by the sodium ion is the opposite of that of potassium; the plasma sodium decreases as potassium rises. Evidently it diffuses from the plasma into the cells.

These changes due to diffusion depend upon the permeability of the cells. The process could be slowed if the increasing permeability of the cells could be retarded. The possibility that ammonia is in some measure responsible for this phenomenon suggests the use of carbon dioxide to slow ammonia production.

Comparison of blood collected under carbon dioxide for changes in potassium, sodium, ammonia-nitrogen, and  $p_H$  with a control specimen withdrawn in the air demonstrated that carbon dioxide is effectual in retarding the changes in the concentration of these bases and maintains the  $p_H$  nearer neutral.

The plasma calcium content remains constant for nine days even when shaken. Magnesium diffuses into the plasma so slowly that the amount accumulated in nine days is too small to have any toxic effect. Moderate trauma does not materially increase the rate.

Of the anions, the fall of plasma carbonates and chlorides and the rise of phosphates are apparently innocuous.

The statistics of reactions following transfusion cannot be briefly presented because of the necessity of detailed information as to criteria and technic.

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However, with these two factors constant, only one difference in the incidence and severity of reaction between fresh citrated and stored citrated blood need be anticipated, namely, jaundice. This is transient and asymptomatic but frequently follows use of blood stored for nine or more days.

The outstanding changes of clinical interest taking place in stored blood are its loss of white blood cells and platelets, its increase in plasma potassium, and decrease in prothrombin. For most purposes it should give results comparable with fresh blood; for infection, prothrombin deficiency, and shock it would be inferior. Intelligently employed during the first week of storage, it need be neither dangerous nor disappointing.

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## STUDIES IN BLOOD PRESERVATION\*

### THE STABILITY OF PLASMA PROTEINS

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THE PREPARATION of an artificial fluid medium which could be used for perfusion experiments was suggested by the French physiologist, Le Gallois, in 1812. To-day, the increasing interest in plasma transfusions signifies a nearer approach to this ideal.<sup>5</sup> The advantages of plasma are many: It is a more stable system than blood; because of its buffer capacity, it is superior to acacia, glucose, and salt infusions; its ionic content is of physiologic proportions; it contains certain organic substances necessary for maintaining protoplasmic irritability; and, in addition, it possesses proteins which are concerned with innumerable functions of the body economy.

In 1871, Bowditch, working in the laboratory of Carl Ludwig, observed the greater efficacy of serum as a perfusion fluid. He saw a frog's heart, which had been arrested by salt, revived by serum.

Ringer at first disagreed that serum possessed any attribute other than that due to the presence of the salts in balanced proportion. Later, however, he admitted that even a frog's heart brought to a standstill by physiologically correct salt solutions could be revived through serum infusions.

Both plasma and serum restore the irritability of protoplasm. This is not peculiar to the vegetable kingdom (a)† but applies also to the heart muscle of both cold (b)† and warm (c)† blooded animals. Other substances share in this restorative action such as milk,<sup>32</sup> gastric juice,<sup>32</sup> digested peptones,<sup>72</sup> milk whey,<sup>28</sup> egg white,<sup>76</sup> and gelatin.<sup>76</sup> Wieland,<sup>98</sup> in 1921, confirmed this action of serum and demonstrated that surface-active agents such as sodium oleate, ether, xylol, camphor, and animal charcoal corrected the hypodynamic state of the excised frog's heart through adsorption of the accumulated metabolic products.

This activating substance is soluble in water or dilute alcohol and is organic in nature. Heating the plasma or cooking the serum lessens the restorative effect.<sup>85</sup> It is not removed by ether.<sup>76</sup> Its widespread distribution in both the vegetable and animal cells is of provoking interest.

To-day, the progressive deterioration of preserved whole blood has become apparent. On the other hand, the stability of preserved plasma is now recognized. There are certain advantages of plasma<sup>93</sup> over whole blood, especially over blood stored too long.<sup>80</sup>

\* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

† (a) Leached *Nitella* cells.<sup>69</sup>

(b) Toad;<sup>72</sup> frog;<sup>7, 26, 32, 42, 45, 52, 57, 62, 70, 76, 85, 91, 98</sup> turtle.<sup>42, 62</sup>

(c) Cat;<sup>27, 28, 45</sup> dog;<sup>36, 45</sup> rabbit.<sup>36, 77</sup>



Amberson,<sup>4</sup> in his review of the literature on blood substitutes, has pointed out some of the advantages of plasma:

*Plasma Is Nonantigenic.*—The acid proteins of the erythrocyte membrane<sup>35</sup> as well as hemoglobin have been shown to be antigenic. For this reason repeated transfusions are at times dangerous. Repeated plasma transfusions have been given without anaphylactic reactions.<sup>33</sup> Thus plasma may be safer than blood.<sup>67</sup>

*Plasma Is Less Toxic.*—There have been many untoward reactions with serum. In dogs, the use of concentrated serum has given rise to shock<sup>2</sup> and to severe chills.<sup>25</sup> The reactions become graver with the use of heterologous sera.<sup>43, 56, 78</sup> In the cat, following such serums, a decrease in blood pressure, together with changes in the liver, kidneys, and lungs has been noted.<sup>8</sup> In rabbits, Rous and Wilson<sup>78</sup> have reported the development of liver necrosis following the injection of horse serum. In man, Ravdin, Stengel, and Prushankin<sup>73</sup> have observed severe reaction following the infusion of lyophilized serum and have cautioned against its use. Strumia, Wagner, and Monaghan<sup>86, 87</sup> have abandoned altogether the use of serum and noted freedom from reactions with plasma. Sudden death in man has been noted after the injection of serum.<sup>11</sup>

What gives rise to this difference between serum and plasma is not known. Brodie<sup>8</sup> suggests that the active substance is a proteid of the albumin class which is coagulated at 86°F. This active substance is only produced when blood clots, and the interaction of the blood corpuscles is necessary in its formation.<sup>8</sup> Serum obtained from plasma is inactive,<sup>8</sup> whereas serum separated after clotting may cause severe reactions.<sup>86</sup>

*Availability.*—Type AB plasma, which is free from agglutinins, or such plasma artificially made by mixing Types A and B bloods and removing the plasma,<sup>14</sup> can always be kept on hand for emergency use. The administration of untyped plasma<sup>16, 48, 86, 87, 88</sup> may not be free from danger,\* especially in those cases where the titer of the plasma is high and the recipient is markedly anemic.<sup>44</sup>

*Storage.*—Whole blood deteriorates rapidly;<sup>80</sup> plasma has been preserved for months.<sup>19, 31, 88</sup> Desiccated plasma carried out by the lyophile process<sup>17</sup> or cryochem-process<sup>20</sup> may extend the period of preservation for years. Whether this will hold true for the plasma dried at body temperature, as recently suggested by Edwards, Kay, and Davie,<sup>14</sup> remains to be seen. These methods concentrate the material which may be given in either dilute or concentrated form.<sup>33, 34</sup>

*Doses.*—Filatov and Kartasevskij<sup>19</sup> use from 150 to 250 cc. of plasma as a hemostatic and 300 to 350 cc. in shock. Strumia, *et al.*, report 500 cc. as the average amount with a range from 250 to 700 cc. in the treatment of shock. Mann<sup>56</sup> recommended a dose of 20 cc. per Kg. Recently, 20 Gm. of the dried powder in 250 cc. of distilled water has been advocated.<sup>14</sup>

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\* Personal communication from Dr. Karl Landsteiner.

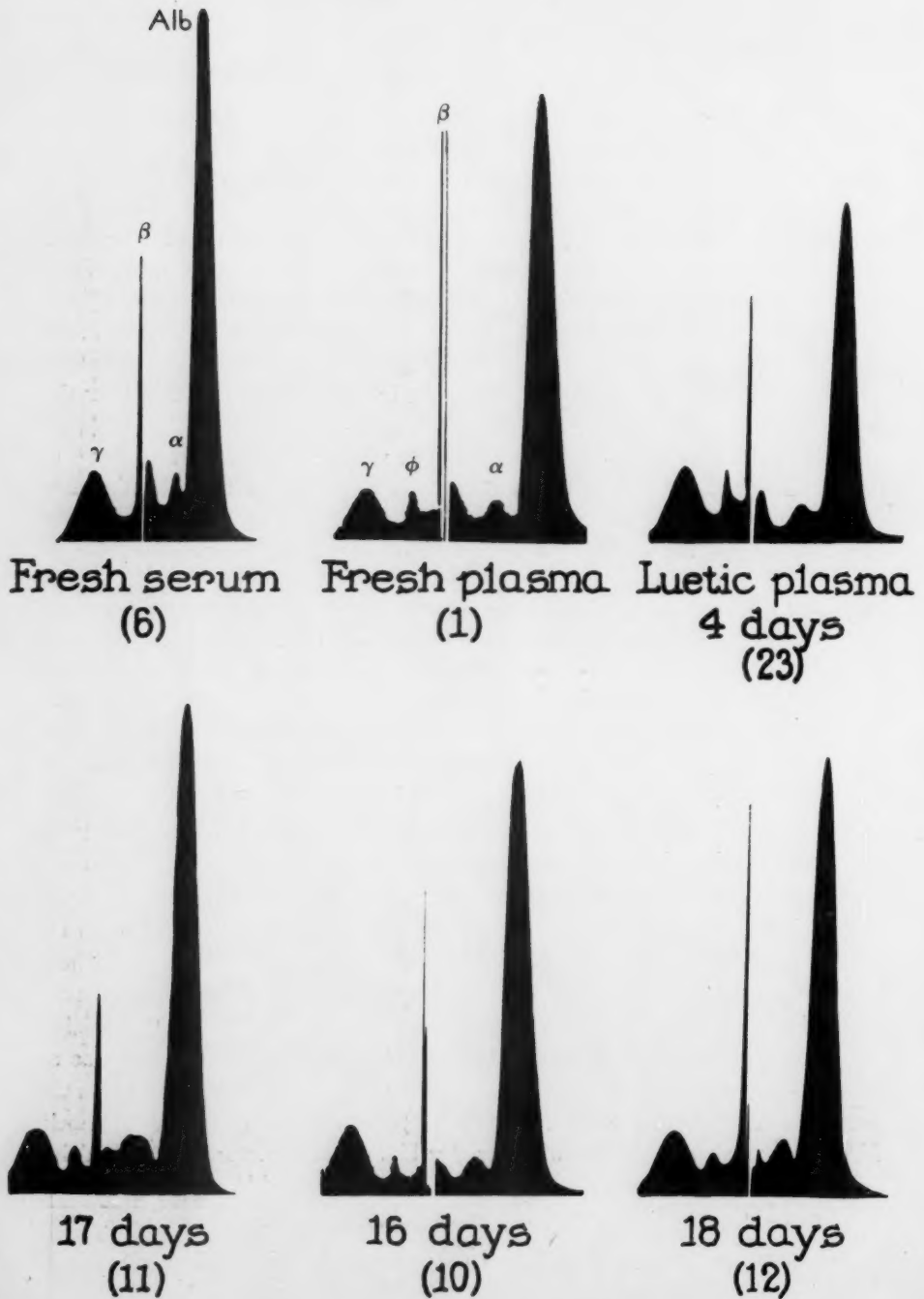
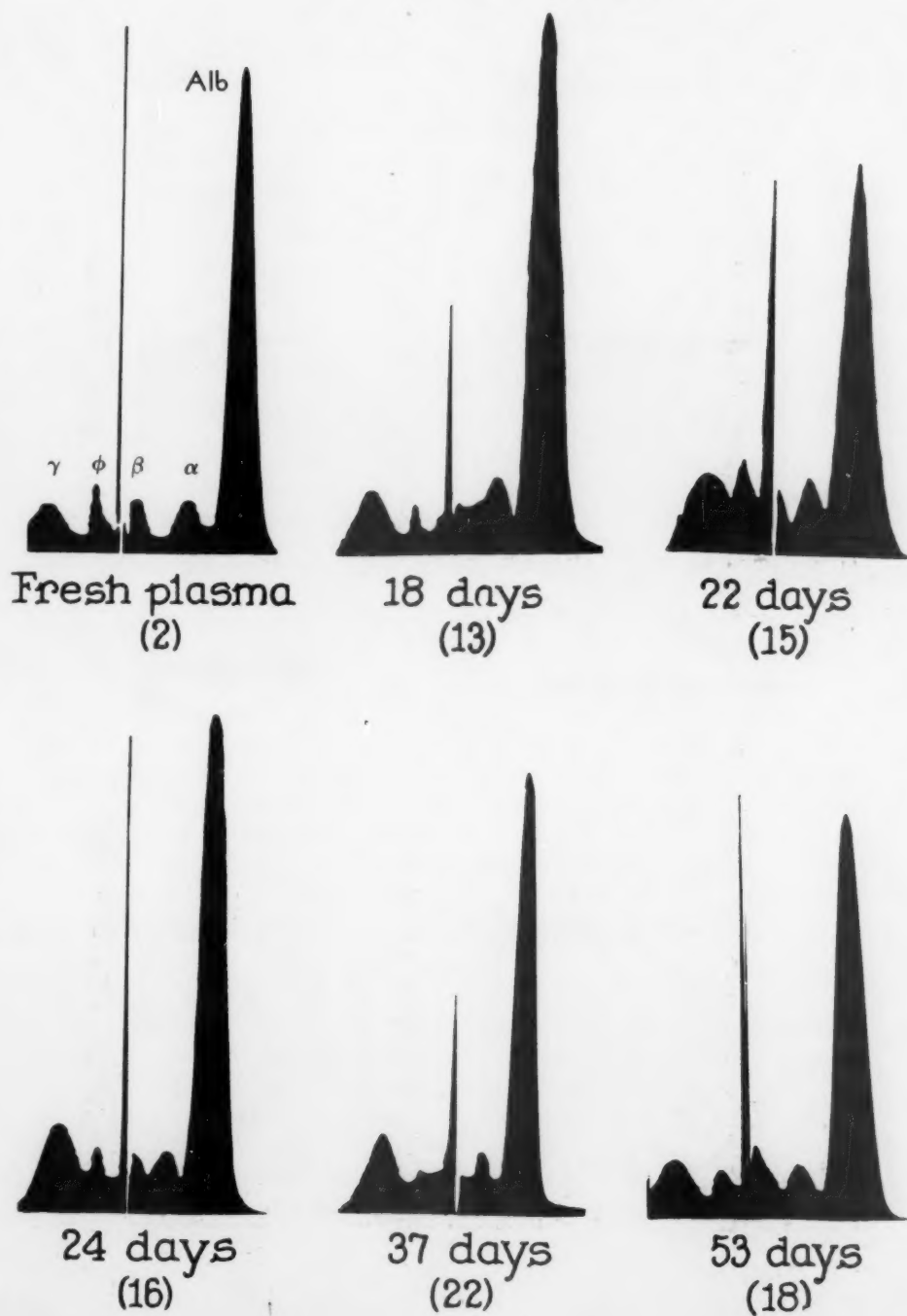
Electrophoretic  
protein patterns

FIG. 1.

## Different refrigerated blood samples



## Normal and pathological serum and plasma

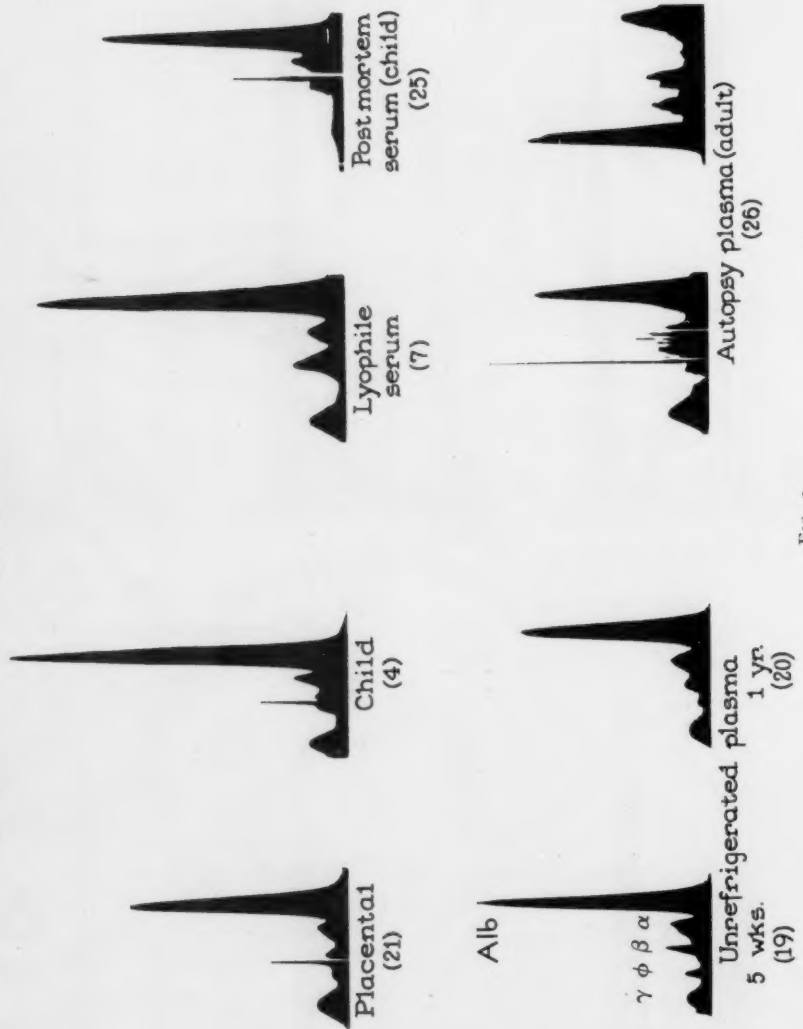


FIG. 2.

## BLOOD PRESERVATION

A few of the functions of plasma proteins are outlined in Table I. The various pathologic conditions benefited by plasma are listed in Table II.

The purpose of this investigation is to reexamine these plasma proteins, and to ascertain which factors govern their stability and enhance their preservation.

TABLE I

### A FEW FUNCTIONS OF PLASMA PROTEINS

Antibody formation.<sup>79</sup>  
Blood pressure increase.<sup>56</sup>  
Blood volume maintenance.<sup>25, 36</sup>  
Capillary permeability control.<sup>12, 13, 41, 82</sup>  
Capillary pressure.<sup>3, 65</sup>  
Capillary tone.<sup>41</sup>  
Clotting.<sup>21-24</sup>  
Diuresis.<sup>3, 34</sup>  
Edema prevention.<sup>63, 65, 94, 95</sup>  
Hematogenesis.<sup>35</sup>  
Immunity.<sup>30</sup>  
Irritability of cardiac muscle restored.<sup>7, 26, 28, 42, 45, 57, 70, 72, 76, 85</sup>  
Irritability of leached *Nitella* cells restored.<sup>69</sup>  
Kidney function, restored in nephrosis.<sup>3, 96</sup>  
Organ culture.<sup>10</sup>  
Protection against drugs.<sup>1</sup>  
Protection against shock.<sup>38, 97</sup>  
Protection against toxins.<sup>64, 97</sup>  
Stabilizing factor.<sup>97</sup>  
Tissue culture.<sup>10</sup>  
Vital.<sup>38</sup>  
Wound repair.<sup>24</sup>

**ALBUMIN.**—Martius<sup>75</sup> attributed to serum albumin the property of restoring cardiac irritability in the perfused frog's heart. This has been disputed.<sup>91</sup> A less disputed fact is that the smaller albumin molecule is four times as active per gram as the globulin in relation to osmotic pressure.<sup>63</sup> Starling<sup>84</sup> established the endosmotic equivalent of albumin as the factor in maintaining capillary pressure. The importance of albumin in edema formation has again been emphasized.<sup>63, 94, 95</sup> Following plasmapheresis, the regeneration of albumin is slow<sup>71</sup> after a short early rise.<sup>83</sup> This may be accelerated by plasma infusion.<sup>94</sup> A reversal of the albumin/globulin ratio is seen in certain disease conditions and in preserved blood.<sup>40</sup>

**GLOBULIN.**—By definition, globulins are those proteins which are insoluble in water but soluble in dilute solutions of neutral salts. In plasma, there are four principal globulin components as judged by mobility determinations. *Alpha* globulin is increased in infections;<sup>51</sup> the increase in *beta* globulin may be due to a labile lipoprotein;<sup>51</sup> the *gamma* globulin is associated with an increase in antibodies; while fibrinogen is associated with clotting. von Ott<sup>70</sup> failed to get good recovery of cardiac irritability with perfusion of globulin through the frog's heart. In contrast to fibrinogen, the reformation of globulin is slow



after its depletion, though faster than albumin.<sup>37, 38, 39, 71</sup> In preserved blood, the increase in the globulin<sup>40</sup> has been attributed to the protein component from the erythrocyte membrane.<sup>35</sup>

TABLE II

## PATHOLOGIC STATES BENEFITED BY SERUM OR PLASMA TRANSFUSIONS

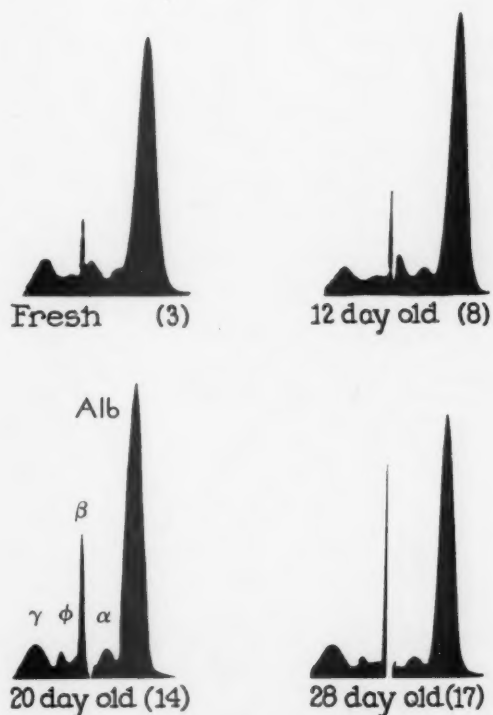
Anemia. <sup>66, 77</sup>
Burns. <sup>14, 15, 18, 19, 29, 55, 92</sup>
Chickenpox. <sup>61</sup>
Cholemia. <sup>19</sup>
Edema. <sup>3, 94, 95</sup>
Hemorrhage. <sup>6, 9, 15, 18, 74, 77, 87</sup>
Bleeding gastric ulcer. <sup>10, 29</sup>
Hemorrhagic conditions. <sup>19, 48</sup>
Hemorrhagic disease of new born. <sup>96</sup>
Postoperative hemorrhage. <sup>87</sup>
Pregnancy. <sup>19</sup>
Hypoproteinemic states. <sup>73, 82, 89, 95</sup>
Increased intracranial pressure. <sup>33</sup>
Infections, acute hemolytic streptococcus. <sup>61</sup>
Intestinal obstruction and strangulation. <sup>87</sup>
Lipoid nephrosis. <sup>3</sup>
Marasmus. <sup>98</sup>
Mumps. <sup>61</sup>
Nephrosis. <sup>34</sup>
Nutritional edema. <sup>94, 95</sup>
Peritonitis. <sup>3</sup>
Prematurity. <sup>96</sup>
Scalds. <sup>14</sup>
Scarlet fever. <sup>61</sup>
Septicemia. <sup>66</sup>
Shock. <sup>6, 16, 18, 44, 47, 48, 55, 56, 99, 99</sup>
Anesthesia. <sup>68</sup>
Cold. <sup>29</sup>
Hemolysis. <sup>31</sup>
Operation. <sup>14, 15, 19, 68</sup>
Toxins. <sup>66</sup>
Trauma. <sup>29, 87</sup>
Wound. <sup>14</sup>
Whooping cough. <sup>61</sup>
Wound repair. <sup>89</sup>

**FIBRINOGEN.**—Of the globulins, this appears to be the most homogenous. Its formation is confined to the liver. Foster and Whipple<sup>21, 22, 23, 24</sup> have demonstrated that tissue injury is the most powerful stimulus to its formation and that, following depletion, its regeneration is complete in 24 hours. This is in contrast to the other globulins. Liver injury definitely delays this regeneration. Diet, especially cooked pig stomach, accelerates its production.<sup>22</sup> With its depletion, celiotomy wounds heal very slowly.<sup>22</sup>

**Electrophoretic Method of Analysis.**—Analysis of the various protein components in plasma have been unsatisfactory because of coprecipitation of

the albumin and globulin fractions. That albumin-globulin separation by the usual "salting out" methods is by no means sharp has been determined by means of the ultracentrifuge.<sup>59, 60</sup> Tiselius demonstrated that the chemical uniformity of a protein could be established through electrophoretic measure-

Electrophoretic patterns  
of preserved plasma  
from same donor



Four blood samples taken at different times; collected in 2.5 per cent sodium citrate and stored in four tubes in electric refrigerator at 4°C. Type A blood

FIG. 3.

ments. Both Longworth<sup>50</sup> and Luetscher,<sup>53</sup> using these measurements of Tiselius,<sup>60</sup> have reaffirmed the inaccuracy of the "salting out" process. With the availability of this exact method, the nature and stability of the proteins in preserved blood can now be determined.

*Procedure.*—Refrigerated plasma samples of varying ages were obtained

TABLE III  
NORMAL PLASMA AND SERUM  
Composition

No.	Material	Composition					Mobilities, $U \times 10^{-5}$							Remarks
		A Per Cent	A/G†	$\alpha/A$	$\beta/A$	$\gamma/A$	$\phi/A$	$p_H$	A	$\alpha$	$\beta$	$\gamma$	$\phi$	
1*	Fresh plasma Type B (J. S.)	4.68	2.00	0.08	0.24	0.08	0.17	7.62	6.54	5.0	3.5	2.0	0.4	1/5 dilution
2	Fresh plasma Type A†	4.35	2.36	0.12	0.15	0.09	0.16	7.78	5.75	4.3	2.6	1.6	0.2	Citrate
3	Fresh plasma Type A (C. R. D.)	3.96	2.27	0.08	0.18	0.08	0.18	7.72	5.95	4.2	2.9	1.6	0.2	Citrate
4	Fresh plasma Type A (child)	4.11	2.56	0.11	0.14	—	0.14	7.57	5.88	4.5	3.0	—	0.3§	Heparin. Oxalate
6	Fresh serum Type B (J. S.)†	4.76	2.11	0.09	0.21	—	0.18	7.80	5.98	4.3	2.5	—	0.3	
7	Lyophilized serum] Type O	5.08	2.17	0.12	0.18	—	0.16	—	6.15	4.5	3.0	—	0.3§	
	Mean	4.49	2.25	0.10	0.18	0.08	0.17							

\* Refers to figure number in illustration.

† A/G calculated on serum basis.

‡ Previously reported.

§ Mobility figured from gamma globulin.

# BLOOD PRESERVATION

from three different Blood Banks in New York City. In addition, unrefrigerated samples were sent for examination from Salisbury, North Carolina. Plasma was obtained also from the autopsy room of the Presbyterian Hospital, and placental plasma from the Sloane Hospital for Women, New York City. The reason for selecting the latter two types of plasma is that such blood has been used for transfusions. To ascertain what effect the lyophile process has on serum proteins, a sample of dried serum was supplied by Dr. I. S. Ravdin from Philadelphia.

*Method.*—The electrophoretic method of analysis of proteins has been reported in detail by Longworth and MacInnes.<sup>49, 50, 51</sup> In brief, a four times diluted portion of plasma is dialyzed in a bag made from cellophane tubing constructed in such a manner as to give a large surface to volume relationship. The buffer with a  $p_H$  at 7.8 to 25° C. consisting of 0.025 M. lithium diethyl barbiturate, 0.025 M. diethyl barbituric acid, and 0.025 M. lithium chloride is used. The dialysis is carried out from 48 to 72 hours in a two liter flask containing fresh buffer at a temperature between 0° and 2° C. in a thermostatically controlled electric refrigerator. During the dialysis some precipitate separates out. It is, therefore, necessary to clear the protein solution in an angle centrifuge operated at 0° C. before its introduction into the electrophoresis cell. The  $p_H$  measurement is determined with the glass electrode of MacInnes and Longworth. The conductivity cell is of special design<sup>51</sup> as well as the screened bridge used for the measurement of electrolytic conductance.<sup>51</sup> The establishment of a Donnan equilibrium is assumed when further dialysis produces no change in conductance of the protein solution and the outside solution has the conductance of the original buffer. The manner of obtaining the protein patterns and of computing the different mobilities of the protein constituents has been published by Longworth, Shedlovsky, and MacInnes.<sup>51</sup>

TABLE IV

	Longworth	Luetscher	This Series	Preserved
Albumin per cent.....	4.38	4.00	4.49	3.73
Albumin/globulin*.....	1.85	2.00	2.25	1.74
Alpha globulin albumin.....	0.12	0.11	0.10	0.12
Beta globulin albumin.....	0.23	0.21		0.23
Gamma globulin albumin.....	0.21	0.18		0.24
Fibrinogen albumin.....	0.09	0.09		0.09
Number of analyses.....	7	?	6	12

\* Estimated on serum basis.

*Results.*—The normal values (Table III) compare with those reported by Longworth, Shedlovsky, and MacInnes, and Luetscher (Table IV, columns 1, 2, 3). In column 4, the mean values for plasma preserved 12 to 53 days are tabulated.

*DISCUSSION.*—In comparing the values for preserved plasma with the values for fresh plasma reported in this series and in others, several points

TABLE V  
PRESERVED NORMAL PLASMA

No.	Material	Age of Blood: Days	Composition					Mobilities, $U \times 10^{-5}$					Remarks			
			A Per Cent	A/G†	$\alpha/A$	$\beta/A$	$\gamma/A$	$\phi/A$	$p_H$	A	$\alpha$	$\beta$		$\gamma$	$\phi$	
REFRIGERATED																
8*	C. R. D. (same as 3)	12	3.81	1.92	0.11	0.21	0.07	0.20	7.71	6.15	4.3	2.9	1.6	0.1	Citrate	
9	Bellevue No. 1827	12	3.76	1.33	0.17	0.28	0.17	0.30	7.81	5.83	4.1	2.8	1.7	0.3	Citrate	
10	Type O															
10	J. S. (same as 1, 6)	16	3.18	1.67	0.11	0.23	0.08	0.26	7.58	—	—	—	—	—	Citrate	
11	Mt. Sinai No. 2845	17	4.22	2.10	0.14	0.17	0.06	0.16	7.83	6.07	4.2	2.9	1.8	0.3§	Citrate (11-day cells)	
12	Bellevue No. 1776	18	3.67	1.67	0.11	0.27	0.09	0.22	7.81	5.82	4.3	2.9	1.7	0.2	Citrate	
13	Type A															
13	H. H. Type A	18	4.08	2.04	0.14	0.17	0.06	0.18	7.57	6.18	4.5	2.8	1.7	0.1	Citrate (collected in CO <sub>2</sub> )	
14	Special bottle															
14	C. R. D. (same as 3, 8)	20	3.66	1.72	0.11	0.21	0.09	0.26	7.73	6.25	4.6	3.2	1.7	0.2	Citrate	
15	Bellevue No. 1737	22	3.58	1.67	0.14	0.21	0.13	0.25	7.78	5.72	4.1	2.9	1.6	0.3	Citrate	
16	Type AB															
16	Mt. Sinai No. 2821	24	4.13	1.75	0.12	0.21	0.08	0.24	7.83	6.06	4.3	3.2	1.7	0.2	Citrate	
17	Type A															
17	C. R. D.	28	2.89	1.54	0.12	0.27	0.08	0.26	7.75	6.18	4.5	3.1	1.7	0.3§	Citrate	
22	(Same as 3, 8, 14)															
22	Bellevue	35	3.72	1.70	0.10	0.22	0.09	0.27	7.67	6.00	4.4	3.2	1.7	0.1	Citrate	
18	Ultracentrifuge															
18	Mt. Sinai†	53	4.09	1.72	0.11	0.25	0.09	0.22	—	5.70	4.0	2.5	1.6	0.1	Citrate	
	Special flask															
Mean			3.73	1.74	0.12	0.23	0.09	0.24								

\* Refers to figure number in illustration.

† A/G figured on serum basis.

‡ Previously reported.

§ Mobility figured from gamma globulin.



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TABLE VI  
PRESERVED PLASMA: NORMAL AND ABNORMAL

No.	Material	Age of Blood: Days	Composition						Mobilities, $U \times 10^{-3}$						Remarks
			A	A/G†	$\alpha/A$	$\beta/A$	$\gamma/A$	$\phi/A$	pH	A	$\alpha$	$\beta$	$\gamma$	$\phi$	
			UNREFRIGERATED												
513 19*	Saline diluted plasma	35	2.64	1.90	0.21	0.12	0.09	0.20	7.82	6.40	5.10	3.5	2.0	0.6	From North Carolina
20	Saline diluted plasma	356	3.33	1.82	0.22	0.13	0.07	0.20	7.80	6.45	4.80	3.3	2.1	0.5	From North Carolina
21	Placental plasma	0	3.47	2.00	0.13	0.16	0.05	0.21	7.85	6.30	4.80	3.0	1.9	0.1	Oxalate
23	Luetic plasma	4	2.50	1.54	0.12	0.21	0.18	0.32	7.85	6.17	4.60	3.1	1.7	0.1	Citrate
25	Autopsy serum (child)	—	4.22	1.92	0.13	0.25	—	0.14	—	—	—	—	—	—	
26	Autopsy plasma	—	3.28	0.96	0.26	0.42	0.07	0.36	—	—	—	—	—	—	

\* Refers to figure number in illustration.

† A/G figured on serum basis.

may be made. The greatest change appears in the decrease of albumin as well as a change in the components which constitute the albumin/globulin ratio. Fibrinogen appears unaltered. A definite increase appears in the *gamma* globulin. This decrease in albumin and increase in *gamma* globulin have been previously noted by Knoll.<sup>40</sup> It is of interest that the two specimens which had been kept in a specially designed bottle<sup>80</sup> showed the least changes.

In comparing the refrigerated samples with those that had been kept at room temperature and had been shipped about the country, the greatest difference is seen in the *beta* globulin fraction. In the diagram, the *beta* globulin disturbance (indicated by the thin spike in the *beta* globulin region) is absent and the *beta* globulin/albumin ratio is decreased.

Both the autopsy serum from the child and the plasma from the adult were abnormal. The placental plasma appeared within normal limits. The lyophilized serum presented an anomaly in that the *beta* disturbance was missing.

No conclusions can be drawn from this small series; certain indications, however, may be followed out: First as to the source of the preserved blood. Postmortem blood appears abnormal; this may not apply to blood collected from those who have met sudden death. Placental blood would appear to be a normal source for conserved blood. Lyophilized serum appears abnormal. Refrigeration seems to enhance the preservation of plasma as did the shape of the flask. Possibly denaturation<sup>99, 100</sup> of plasma proteins is slower under these conditions.

#### SUMMARY

(1) The relationship of plasma to irritability of both vegetable and animal cells is reviewed.

(2) Plasma approaches the ideal physiologic perfusion fluid, and is superior to acacia, glucose, salt, and serum.

(3) Electrophoretic patterns of six normal, 14 preserved, and four miscellaneous plasmas are presented.

(4) Refrigerated plasma appears to be stable and shows only minor changes up to 53 days' storage. The A/G ratio declines, due principally to a decrease in the albumin component.

(5) Unrefrigerated plasma, lyophilized serum, and autopsy plasma appear definitely abnormal.

Appreciation is herewith expressed to Dr. D. A. MacInnes for both his help and encouragement in the conduction of these studies, and to Drs. L. G. Longworth and T. Shedlovsky for their aid and cooperation as well as for permission to use some of their material. To the authorities in charge of the Blood Banks at the Mt. Sinai, Bellevue, and Presbyterian Hospitals, in New York, a debt of gratitude is expressed for the supply of the various plasmas tested. For the donation of the unrefrigerated plasma specimens which were shipped to us from Salisbury, North Carolina, by Dr. J. Elliott, acknowledgment is here made. The lyophilized serum was supplied to us through the kindness of Dr. I. S. Ravdin, of Philadelphia. The opportunity to conduct these studies

was made possible through a Fellowship from the Commonwealth Fund, New York. In part, the expenses of this investigation were defrayed through a grant from the Blood Transfusion Betterment Association, New York.

In conclusion, this program of work, its direction and fulfillment are a part of the investigative work sponsored by Dr. Allen O. Whipple, of the College of Physicians and Surgeons, Columbia University, New York.

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\* See illustration on page 519.

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### Electrophoretic patterns of same plasma

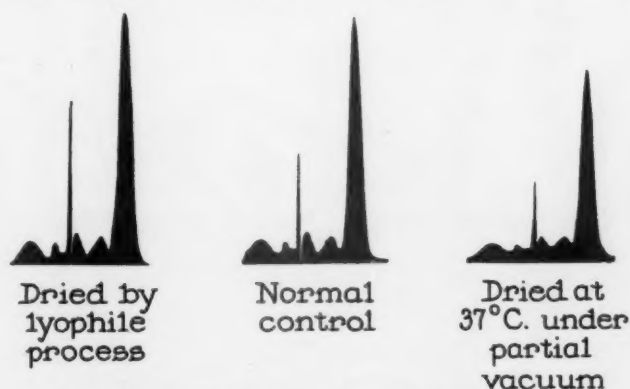


FIG. 4.—Plasma dried according to method of Edwards, Kay and Davie<sup>14</sup> on the right hand side. Note the difference between this and the other two.

## SODIUM CHLORIDE METABOLISM OF SURGICAL PATIENTS\*

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THREE CONDITIONS may materially alter the sodium chloride metabolism of the surgical patient from that of the normal: (1) A reduction in the intake of salt through inability to take anything by mouth; (2) the frequent occurrence of abnormal losses of fluid containing salt; and (3) a tendency for the retention of salt and water when the patient is seriously ill and the intake of salt has been excessive. With these conditions in mind, sodium chloride therapy is best handled with a knowledge of the fundamental processes involved.

*Normal Sodium Chloride Metabolism.*—Sodium chloride is the most abundant electrolyte in the blood and interstitial body fluid, while for intracellular fluids, potassium and phosphate are the chief ions.<sup>1, 2</sup> Sodium chloride has two vital functions: (1) It helps to maintain the acid base balance of the body; and (2) it is largely responsible for the total osmotic pressure of the extracellular fluids. Gamble<sup>2, 3</sup> has aptly pointed out that the electrolytes really sustain the blood and interstitial fluids, and while one's attention is frequently drawn to other substances, such as the blood sugar, the amino-acids, the lipids, and the nitrogenous waste products, these are simply the nutrient or waste materials being transported to and from the cells by their real environment of salt solution. And further, while the volume of the extracellular vehicle fluid is dependent upon the amount of the electrolytes, Gamble and Ross<sup>4</sup> have pointed out that sodium ions are more important than chloride ions in this regard, since sodium cannot be replaced by any other anion while chloride loss can be replaced by bicarbonate ions formed from the carbon dioxide of catabolism. A preponderant loss of sodium thus leads to greater dehydration than a predominate loss of chlorides.

The normal balance of sodium chloride is maintained by a daily intake of from 1 to 2 Gm. in the food itself<sup>5</sup> and from 2 to 8 Gm. added in the process of cooking and the vigorous use of the salt shaker at the table. To this oral ingestion, from eight to ten liters of salt-containing solution, made up of gastric juice, bile, pancreatic secretion, and succus entericus, are poured into the upper part of the intestinal tract daily. Body economy is shown by the fact that 95 per cent or more of the sodium chloride is absorbed lower down in the intestinal tract, and the daily salt loss in the stool

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## SODIUM CHLORIDE METABOLISM

is normally less than 0.5 Gm. a day.<sup>5, 6</sup> Important amounts of sodium chloride are normally excreted by the body in two ways. One is through the sweat glands and varies with their activity. With insensible perspiration insignificant losses of salt occur, Freyberg and Grant<sup>7</sup> having reported from 0.25 to 0.41 Gm. per day. Active sweating has produced excretions as high as 2 Gm. an hour,<sup>8</sup> but this is exceptional. It has been shown that an adaptation to extreme dry heat takes place, and the salt loss in sweat is much reduced.<sup>9</sup> The kidneys maintain the salt balance by excreting the excess intake, and they usually put out from 3 to 8 Gm. of sodium chloride a day. This is but one example of the kidneys' important function of maintaining a certain concentration of substances in solution in the body fluids, and excreting the remainder.

To provide some salt to patients taking nothing by mouth and, therefore, requiring parenteral fluids, we believe that if no abnormal losses of sodium chloride have occurred, each patient should be given half a liter of Ringer's solution daily, and the remainder of the fluid needs should be supplied by 5 or 10 per cent dextrose in distilled water. The 4 to 5 Gm. of sodium chloride thus given will provide for daily metabolic needs and adjustments and at the same time will avoid edema from excess salt.

*The Conservation of Electrolytes by the Body.*—The observations of many workers<sup>3, 5, 10, 11, 12</sup> have shown that when no sodium chloride is taken in or when the balance is disturbed by abnormal losses, as in vomitus, the kidneys reduce this excretion to a minimum and conserve salt. Our associates, Bartlett, Bingham and Pedersen,<sup>13</sup> found the fact well demonstrated in their experimental production of hypochloremia in humans. Benedict,<sup>14</sup> in 1915, reported the chloride excretion in the urine of a subject who fasted for 31 days, and found that 12.3 Gm. of chloride or 20.3 Gm. of sodium chloride were put out during that time. Half of this amount was excreted in the first four days; during the later days only traces of chloride were found in the urine.

In the practical handling of surgical patients it can be assumed without chemical studies that their sodium chloride concentration will be normal if the patient has been eating a good, general diet and has had no abnormal losses of salt containing fluid. Because of the conservation of electrolytes by the kidneys, one can go a step further and assume that a surgical patient who has been on a restricted diet but who has not been losing salt abnormally will have approximately normal plasma chlorides and sodium. These practical considerations are unconsciously used every day since we do not carry out plasma chloride and sodium determinations on every surgical patient.

*Abnormal Salt Losses.*—One looks among surgical patients for depleted sodium chloride when significant amounts of electrolyte containing fluid have been lost abnormally from the body by vomiting, diarrhea, drainage from intestinal, pancreatic or biliary fistulae, profuse serous or wound secretions, and prolonged sweating. O'Shaughnessy,<sup>15</sup> in 1831, recognized that in cholera important amounts of alkaline substance disappeared from the

blood and were present in the profuse dysenteric excretions. Thomas Latta,<sup>16</sup> in the same year, first administered saline solution intravenously to patients with this disease, but was discouraged with the result because the amount injected was too small, the injection was given too late, or the effect was offset by the presence of other disease. Rogers<sup>17</sup> worked incessantly on the problem of restoring alkali deficit in cholera patients, and, in 1916, reported a reduction in the mortality of the severe cases with uremia from 11.1 to 2.7 per cent through the administration of hypertonic solutions of sodium bicarbonate and salt.

In considering intestinal obstruction it would be irreverent not to mention Hartwell and Hoguet,<sup>18</sup> who first showed that dogs vomiting because of intestinal obstruction could be kept alive for many days if treated by large amounts of normal saline solution. Among the surgeons, the subsequent contributions of Orr and Haden<sup>19</sup> were most important in spreading the knowledge of the abnormal chemistry of this disease.

In order to carry out the proper treatment it is important to understand the variations that occur when fluid is lost from different parts of the gastrointestinal tract. With pyloric obstruction the vomitus is predominantly acid and one finds the plasma chlorides decreased and the carbon dioxide combining power increased, giving in the advanced cases the typical chemistry of alkalosis. A satisfactory calculation of the saline solution needed for correction to normal can be made on the basis of the "clinical rule" developed by Coller, Bartlett, Bingham, Maddock and Pedersen:<sup>13,20</sup> "For each 100 mg. that the plasma chloride level needs to be raised to reach the normal (560 mg. per cent) the patient should be given 0.5 gram of sodium chloride per kilogram of body weight." With obstruction of the small intestine, and consequent vomiting, the loss of fluid is a combination of the acid gastric juice and the alkaline bile, pancreatic secretion and succus entericus. The resulting chemistry usually shows a low plasma chloride and a moderately reduced carbon dioxide combining power, which signifies a very definite loss of both chloride ions and base. Usually, the chloride loss is greater than the sodium loss, so it has been feasible in these cases also to use the "clinical rule" as a practical calculation of the amount of sodium chloride needed in the way of physiologic saline or Ringer's solution for correction of the water and electrolyte imbalance.

It can well be added here that when vomiting takes place in the hospital because of pyloric or intestinal obstruction, modern surgical practice requires intubation of the gastro-intestinal tract<sup>21, 22</sup> and, thus, the withdrawal of the fluid and gas from the distended parts. Replacement of the water and electrolytes so removed by giving a volume of physiologic saline or Ringer's solution equal to the drainage has been found to be successful.<sup>13, 20, 23</sup>

Drainage of bile from tubes in the common bile duct is an occasional source of gastro-intestinal fluid loss, and the electrolyte concentration of such bile resembles serum very closely.<sup>5</sup> There are a few more basic than acid ions present, but the difference is not sufficient to make impractical replace-



ment methods calculated from the chloride loss.<sup>13, 20</sup> When the bile drainage is measured daily, as it should be, "volume-for-volume" replacement with physiologic saline or Ringer's solution is effective in maintaining normal blood electrolyte levels. Often the required salt can be given by mouth and there is no need to administer saline parenterally.

Various other methods for restoring and maintaining a normal water and electrolyte balance have been developed,<sup>24, 25, 26, 27</sup> and are being put to the test of practical use. All are indicative of the surgeon's desire to know more about the chemical abnormalities of the diseases under his charge and all have contributed in one way or another to the care of the seriously ill patient.

Ileostomy drainage and diarrhea are not of common occurrence among surgical patients, but occasionally require attention. In such cases the base loss is greater than the chloride loss, so one finds a low carbon dioxide combining power and a close to normal plasma chloride. Occasionally concomitant vomiting also reduces the chlorides. The pediatricians have dealt extensively with the fluid and electrolyte loss associated with diarrhea, and Hartmann<sup>28</sup> has evolved a formula for water and electrolyte correction for such cases. Palmer and Van Slyke,<sup>29</sup> in 1917, developed a line chart for estimating the sodium bicarbonate required in alkali deficits.

Although the surgeon is dealing chiefly with upper alimentary tract losses which generally have an excess of chloride ions and the pediatrician is at the other end of the canal and deals with excess base loss, Gamble<sup>2, 3, 30</sup> has repeatedly emphasized that the same two solutions will, in the vast majority of cases, correct the electrolyte imbalance associated with losses from either end of the canal. Physiologic saline solution provides the essential substances, which are water and sodium chloride ions, for the correction, while 5 per cent dextrose solution in distilled water provides carbohydrates for many purposes and an excess of freely available water for kidney function, whereby the less needed ions are excreted and correction of the electrolyte pattern takes place.

*Edema from Too Much Salt Solution.*—Edema in surgical patients has been discussed particularly by Matas,<sup>31</sup> Jones and Eaton,<sup>32</sup> Coller and his associates,<sup>23, 33</sup> Ravdin and his associates,<sup>34, 35</sup> Curphy and Orr,<sup>36, 37</sup> and White, Sweet and Hurwitt.<sup>38</sup> It seems important here to stress that its occurrence is nearly always the surgeon's error. By way of emphasizing the possible mistake, it is fitting to point out the analogy between edema in nephritis, which is so generally known, and edema in the sick surgical patient, since the conditions for both are somewhat the same.

Page,<sup>39</sup> in a summary of Bright's disease, states: "Most evidence does not support the belief that the ionic excretory power of the kidneys in nephrotic patients is qualitatively different from kidneys of normal persons." He further states: "A number of different factors are responsible for the occurrence of nephrotic edema, the better understood and possibly more important among these being: (1) Hypoproteinemia with consequent loss of

osmotic attraction of the plasma for water; and (2) the hydropigenous effect of salt in the tissues." These two factors are commonly present in the sick surgical patient; the first one may well be beyond the surgeon's control, the second is entirely in his hands. The vast majority of surgical patients have merely a local lesion with no or comparatively little disturbance of their general condition. On the other hand, the sick surgical patient is more seriously ill, most commonly because of one or both of two conditions—malnutrition and sepsis. Frequently, also, there is hepatic and renal damage and possibly severe acute or chronic hemorrhage. These factors often produce hypoproteinemia and thus predispose to the retention of water. Salt comes into the picture through the frequent need for parenteral fluids by the sick surgical patient, and the surgeon's common error of administering fluids as salt solution whether sodium chloride is needed or not. Thus, both in the nephritic and the sick surgical patient, there is the tendency to develop edema and all that is needed to precipitate it is sodium chloride, of which the sodium ion is the most important. The dependence of generalized edema upon a supply of salt solution is worth further emphasis. Shelburne and Egloff<sup>40</sup> produced hypoproteinemia in dogs by plasmaphoresis, and found pitting edema present without the excessive use of water or sodium chloride when the plasma proteins fell to about 3 Gm. and the albumin to 1 Gm. per 100 cc. Then, it is important to note, large amounts of distilled water by stomach tube failed to increase the edema or the weight of the animal. When sodium chloride was also given, 13 Gm. per day, massive edema appeared. Weech, Snelling and Goettsch<sup>41</sup> and Lepore<sup>42</sup> also emphasized that the edema associated with hypoproteinemia is a sodium chloride edema, and the general opinion is that the lower the serum proteins the less sodium chloride it takes to produce edema. DeWesselow<sup>43</sup> states: "Balance experiments show that approximately a liter of water is retained for every six to seven grams of sodium chloride that accumulate in the body, a normal concentration of about 0.6 per cent of sodium chloride being thus preserved in the body fluids and plasma."

Without having serum proteins down to the "critical level" of Moore and Van Slyke,<sup>44</sup> at which nephritics tend to develop edema, the sick surgical patient will develop edema, but generally the latter receives more salt solution. Coller, Dick and Maddock<sup>33</sup> and Curphy and Orr<sup>37</sup> had several instances of this fact in their studies of edema in surgical patients.

Of practical consideration is the fact that when edema is found in a surgical patient the first thought should be, "How much salt solution has this patient received and what are the serum protein values?" The surgical staff may well feel guilty when some patients come to autopsy with waterlogged tissues.

Salt retention and edema have been found associated with medical conditions in which sepsis is present. The best studied of these is that occurring with lobar pneumonia,<sup>5</sup> there being retention during the height of the illness and an outpouring of both salt and water with the crisis. Wilder and Drake<sup>45</sup>

have warned against excess salt solution for such patients. Of the 19 infants studied by them, the three deaths that occurred were in the group of five infants who received large amounts of salt in their diet and developed extensive edema of their tissues.

In summary, it appears that the healthy individual can ingest and excrete about 35 to 40 Gm.<sup>5</sup> of sodium chloride a day. This limit is greatly lowered in sick surgical patients by malnutrition, sepsis, hemorrhage, profuse wound drainage, severe renal and hepatic disease, long operations, and long anesthesia, and it seems that the more pronounced these findings the greater is the retention of salt and water.

*Blood Sodium Chloride Concentration No Index of Excessive Salt Retention.*—With the established fact that excessive salt administration in the sick surgical patient leads to edema, it would be extremely handy if the plasma chloride or sodium level would increase proportionately to the salt retained and be an index of the excessive administration. Such is not the case. In the 26 surgical patients with demonstrable edema, studied by Jones and Eaton,<sup>32</sup> only six had plasma chlorides above the upper limit of normal of 630 mg. per 100 cc.,<sup>5</sup> and only one was above the 700 mg. level. In spite of the edema, most of the chloride values were within the normal range, but one patient had definite hypochloremia. When edema develops, the retained fluid is largely in the interstitial compartment. DeWesselow<sup>43</sup> states the fact well by saying: "The result of salt retention is hydremia, rather than hyperchloremia."

*The Paradox of Low Blood Electrolytes with Edema.*—In the previous paragraph the occurrence of hypochloremia in the face of excessive salt administration to the point of edema was mentioned. The paradox should be emphasized because it can be a trap for the unwary, and the continued attempt to raise the plasma chlorides in some instances can do the patient harm.

In our experience with quantitative methods for the replacement of lost electrolytes we noted that after having given amounts of Ringer's solution calculated from the "clinical rule" to be necessary to raise the plasma electrolytes to normal, two results occurred.<sup>23</sup> The patients with a recent loss of electrolytes from the vomiting of an acute illness, such as an incarcerated inguinal hernia, and whose general condition was fairly good, had a prompt return of their chemistry to normal. On the other hand, patients with a more chronic or severe illness, such as an obstructing duodenal ulcer or with peritonitis, often failed to have their blood electrolytes reach normal. These patients often had lowered plasma proteins because of malnutrition and sepsis. They excreted very little of the given sodium chloride in the urine, and they gained weight. If more Ringer's solution was given the result was simply more gain in weight. If their general condition improved, and they began to eat, then the retained water and salt readjusted, the urine output increased and the blood electrolytes rose to the normal.

A quite apparent example of the uselessness of excessive salt solution while a patient is seriously ill occurs in cases of generalized abdominal car-

cinomatosis with ascites. Bartlett, Bingham and Pedersen,<sup>13</sup> in our laboratory, had a good example of one such case in their study of the salt balance in surgical patients. With abdominal carcinomatosis there is usually low plasma protein because of malnutrition, and the plasma electrolytes are low because they have been taken from the blood and interstitial fluid for the formation of the ascitic fluid. An administration of saline solution parenterally to raise the plasma electrolytes generally results in only a very temporary elevation followed by a decrease and a concomitant increase in the ascites. There are other circumstances in which a similar transfer of fluid and substance is particularly harmful and at this time we wish to comment on data available from patients with severe burns.

Davidson,<sup>46</sup> who introduced the modern tannic acid treatment of burns, found low plasma chlorides and a retention of chlorides during the acute burn reaction and a marked urinary excretion of chlorides and water at about the time the crust was separating. Where some of this sodium chloride goes to is not difficult to answer, considering the extensive edema at the burn site, which Underhill and his associates<sup>47</sup> first studied extensively and demonstrated to be approximately the same as blood plasma. Blalock and his associates,<sup>48, 49</sup> and Harkins<sup>50, 51</sup> studied the development of shock with such plasma losses, and also noted the extensiveness of the depleted plasma proteins. The evidence is that saline or other crystalloid solutions at the time of shock rapidly leave the vascular compartments and carry away more plasma proteins. Beard and Blalock<sup>49</sup> had the impression that their animals with shock died sooner if saline solution was given than if they were left alone. They state their practical opinion by saying: "We do not mean to imply if a patient is in shock as the result of any injury and no donor is obtainable that saline or similar solutions should not be injected. However, in the absence of a favorable response in the blood pressure after a considerable amount of solution had been injected, almost certainly, the further administration of the same fluid intravenously would diminish the chances of recovery." The need for whole blood or plasma transfusions to treat burn shock is apparent and has been advocated by several workers.<sup>52, 53, 54, 55, 56, 57</sup> Trusler, Egbert and Williams<sup>58</sup> recently reported transfusions alone to save their experimental animals from critical burn shock.

In the shock period of the severely burned, transfusions are needed, and no more than moderate amounts of saline solution, three to four liters for an adult, are of possible value, while more may do harm. Add to this the chance that salt solution later on may cause extensive edema because hypoproteinemia and sepsis are likely to be present, then one can understand the caution to give salt solution sparingly to burn patients. We do not agree at all with the recent statement of Darrow<sup>59</sup> that "physiologic solution of sodium chloride, interstitial salt solution or lactate-Ringer's solution must be given in maximum amounts in extensive burns." Hypochloremia may persist in an extensive burn case even after considerable salt has been given and may lead the unwary to give more salt. Trusler, Egbert and Williams<sup>58</sup>



reported a severe burn case in a two-year-old girl and found blood chlorides of 140 mg. per 100 cc. at the time of extensive general edema. This patient developed convulsions and died. Multiple transfusions saved the life of their 15-year-old burn patient, but even for her, generalized edema developed from the continued use of salt solution.

We have repeatedly pointed out that when parenteral therapy is needed, the fluid administered should be chosen to meet the needs of the individual case. When plasma proteins are low, when sepsis is present, salt solution will be abnormally retained and the resulting edema has caused the death of patients. The modern surgeon must be more than a diagnostician and an operator. He must understand the chemistry involved in his serious cases and treat the patient accordingly. Parenteral therapy is merely a means of tiding a patient over a period of crisis. There is no substitute for a good general diet and the sooner the patient is able to eat, the sooner he will get well.

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## FLUID, SALT, AND NUTRITIONAL BALANCE IN PATIENTS WITH INTESTINAL SUCTION DRAINAGE \*

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THE PROBLEM of fluid, mineral, and nutritional balance in patients during gastro-intestinal suction has been of great interest and has caused much concern. In fact, many discussions referring to adequate balances in surgical patients have made note of the difficulties imposed by the patient with suction drainage. Despite this fact, complete quantitative studies concerning this difficulty are hard to find. Paine and Armstrong<sup>1</sup> studied chloride and fluid balances in cases with gastric and duodenal suction drainage and found that there was marked loss of chloride. All authors agree that during suction drainage there is great need for careful attention to fluid and salt balance and indicate that maintenance of this balance may be effected only by parenterally administered fluids.

Since the introduction of intestinal suction drainage by the use of balloon-tipped tubes,<sup>2</sup> we have been impressed by the fact that oral administration of food, fluid, and salt is not only practical but exceedingly important in the care of patients subjected to this procedure. In addition to the advantages nutritionally, patients eating and drinking are happier and tolerate the tube more readily.

Our studies are concerned with four patients (Fig. 1), two with constant suction drainage applied in the lower reaches of the ileum, and two just below the duodenojejunal fold. In all instances intubation was carried out because of small bowel distention. Of the two with the tube tip in the ileum, one (M. H.) had partial obstruction about a foot and a half above the ileocecal valve, the other (J. K.), a partial obstruction in the rectosigmoid. Of the two cases with high jejunal aspiration, one (M. C.) had a ruptured appendix with associated small bowel distention; the other (C. J.) had marked small bowel distention, the cause of which we have not been able to determine by localization or other studies. All of the cases, except the last (C. J.), were subjected to operation and the diagnosis confirmed.

Complete measurements of intake and output were made of all materials directly measurable and separate analyses carried out in duplicate or triplicate. None of these studies were undertaken by the routine hospital labora-

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tory but were subjected to critical investigation in our research laboratory. In order to approach the degree of accuracy we felt necessary for this study,

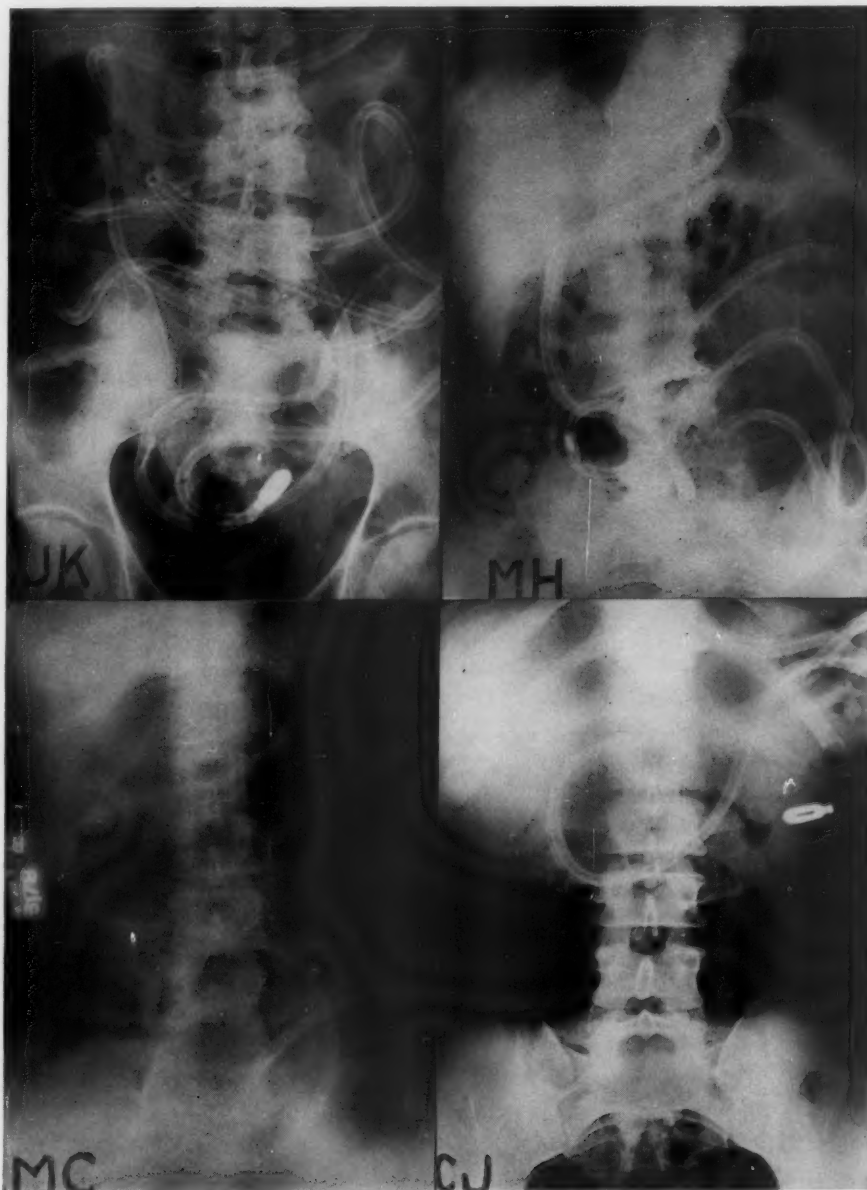


FIG. 1.—Level of drainage in four cases studied, determined roentgenologically every few days.

the collection of materials was made by a nurse especially assigned to this duty. Intake of food was determined by weighing the diet before and after serving, and an equivalent of the food eaten by the patient weighed and

placed in a separate receptacle for drying, ashing and analysis.\* No attempt was made to estimate either water of oxidation or the so-called insensible loss. Regarding the insensible loss, it is worthy of note that with the exception of one patient, for a few days, fever was not a factor of importance.

Serum protein concentrations were calculated from total nitrogen determinations by the micro-Kjeldahl method after subtraction of the nonprotein nitrogen. Carbon dioxide combining capacity of the serum was determined by the method of Van Slyke, *et al.*<sup>3</sup> The method of Wilson and Ball<sup>4</sup> was used for the determination of chloride. Potassium was determined by a chloroplatinic acid procedure modified for use with a photoelectric colorimeter.<sup>5</sup> Sodium was determined by the method of Hoffman and Osgood.<sup>6</sup> All food and fecal samples were dried to constant weight in an oven at 80° C. in order to estimate the water content. Samples of the dried food and feces were ashed in a muffle furnace at 400° F. for the determination of sodium, potassium, and chloride. Separate samples were wet-ashed with sulphuric acid and selenium oxychloride for the determination of total nitrogen.

The simplest and most important studies for the determination of fluid balance in the usual surgical patient are obtained from a measure of the fluid taken by the patient through all routes, and that lost through urine, vomitus, suction drainage, feces, and from fistula. In addition, the volume of urine offers a fairly reliable means of estimating the degree of hydration of the patient. With patients subjected to suction drainage a comparison of the amount ingested by mouth and that aspirated by suction offers a fair estimate of the amount of fluid absorbed through the intestinal tract. Since we have been allowing patients with suction drainage to eat a full diet and drink all they desire, unless there are complications which prevent this, we have been impressed by the excess of intake over drainage in many patients. Since we allow solid food immediately the tube is at the ligament of Treitz, it has been of interest to note that even at this level the intake frequently exceeds that aspirated if the intestine has been decompressed. It is not usual for the patient with distention to care to eat, so we are not concerned, as a rule, with too early intake of solid food. With distention present, it is rare that we note a positive balance in oral intake over materials aspirated.

In this study the oral intake as compared with the aspirated fluid in all cases revealed that varying amounts of food, fluid, and salt were utilized by the patient despite constant suction drainage. The difference between oral intake and suction drainage is markedly affected by the amount of food and fluid that the patient is able to take and the efficiency of the suction for drainage, as well as the ability of the patient to absorb the material. It is only in regard to the greater absorbing surface afforded by the length of intestine above the tube tip that low ileal drainage affords better possibilities for oral feedings. Our data show excellent nutrition and fluid balances for

\* We wish to thank Mrs. Marie Diton, dietitian, Detroit Receiving Hospital, for her cooperation in determining the amount of food consumed by these patients.



# NUTRITIONAL BALANCE WITH SUCTION DRAINAGE

TABLE I  
FLUID BALANCE STUDIES OF J. K. FOR NINE-DAY PERIOD

J. K. - FLUIDS

DATE	16-17	17-18	18-19	19-20	20-21	21-22	22-23	23-24	24-25	TOTALS
INTAKE										
BY VEIN	500	0	0	500	0	0	0	0	0	1000
BY MOUTH	3970	3820	4510	3850 +800	4100	3240 +700	4240	5000	4470	37200 +1500
OUTPUT										
BY TUBE	490	740	250	660	610	640	600	230	250	4570
BY FECES	0	0	0	500	0	500	0	0	0	1010
BY URINE	1080	1730	2460	2740	1900	2000	3000	3040	2230	20180
BALANCE										
ORAL IN - SUCTION	3480	2980	4260	3190	3490	2600	3640	4770	4220	32630
TOTAL INTAKE	4470	3820	4510	5150	4100	3940	4240	5000	4470	39700
TOTAL OUTPUT	1570	2570	2710	3900	2510	3150	3600	3270	2480	25760
TOTAL IN - TOTAL OUT	2900	1250	1800	1250	1590	790	640	1730	1990	13940
BLOOD										
HEMATOCRIT % CELLS		30.4		30.8			35.2			
SERUM PROTEIN GMS. PER 100 cc.		7.28		7.35			7.16			

TABLE II  
CHLORIDE BALANCE STUDIES OF J. K. FOR NINE-DAY PERIOD

J. K. - CHLORIDE

DATE	16-17	17-18	18-19	19-20	20-21	21-22	22-23	23-24	24-25	TOTALS
INTAKE										
BY VEIN	1770	0	0	1770	0	0	0	0	0	3540
BY MOUTH	5560	5180	3650	2580	3350	5550	3300	2780	2520	34470
OUTPUT										
BY TUBE	1890	2820	400	2380	650	2680	760	620	630	12830
BY FECES	0	0	0	300	0	60	0	0	0	360
BY URINE	910	1080	2350	4060	3180	3090	4650	2880	1930	24130
BALANCE										
ORAL IN - SUCTION	3670	2360	3250	200	2700	2870	2540	2160	1890	21640
TOTAL INTAKE	7330	5180	3650	4350	3350	5550	3300	2780	2520	38010
TOTAL OUTPUT	2800	3900	2750	6740	3830	5830	5410	3500	2560	37320
TOTAL IN - TOTAL OUT	+4530	+1280	+900	-2390	-480	-280	-2110	-720	-40	+690
BLOOD										
SERUM CHLORIDE M. EQ. PER LITER		107.5		115.2			105.9			

placed in a separate receptacle for drying, ashing and analysis.\* No attempt was made to estimate either water of oxidation or the so-called insensible loss. Regarding the insensible loss, it is worthy of note that with the exception of one patient, for a few days, fever was not a factor of importance.

Serum protein concentrations were calculated from total nitrogen determinations by the micro-Kjeldahl method after subtraction of the nonprotein nitrogen. Carbon dioxide combining capacity of the serum was determined by the method of Van Slyke, *et al.*<sup>3</sup> The method of Wilson and Ball<sup>4</sup> was used for the determination of chloride. Potassium was determined by a chloroplatinic acid procedure modified for use with a photoelectric colorimeter.<sup>5</sup> Sodium was determined by the method of Hoffman and Osgood.<sup>6</sup> All food and fecal samples were dried to constant weight in an oven at 80° C. in order to estimate the water content. Samples of the dried food and feces were ashed in a muffle furnace at 400° F. for the determination of sodium, potassium, and chloride. Separate samples were wet-ashed with sulphuric acid and selenium oxychloride for the determination of total nitrogen.

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BY URINE	1080	1730	2460	2740	1900	2000	3000	3040	2230	20180
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BLOOD										
HEMATOCRIT % CELLS		30.4		30.8			35.2			
SERUM PROTEIN GMS. PER 100 cc.		7.28		7.35			7.16			

TABLE II  
CHLORIDE BALANCE STUDIES OF J. K. FOR NINE-DAY PERIOD

J. K. - CHLORIDE

DATE	16-17	17-18	18-19	19-20	20-21	21-22	22-23	23-24	24-25	TOTALS
INTAKE										
BY VEIN	1770	0	0	1770	0	0	0	0	0	3540
BY MOUTH	5560	5180	3650	2580	3350	5550	3300	2780	2520	34470
OUTPUT										
BY TUBE	1890	2820	400	2380	650	2680	760	620	630	12830
BY FECES	0	0	0	300	0	60	0	0	0	360
BY URINE	910	1080	2350	4060	3180	3090	4650	2880	1930	24130
BALANCE										
ORAL IN - SUCTION	3670	2360	3250	200	2700	2870	2540	2160	1890	21640
TOTAL INTAKE	7330	5180	3650	4350	3350	5550	3300	2780	2520	38010
TOTAL OUTPUT	2800	3900	2750	6740	3830	5830	5410	3500	2560	37320
TOTAL IN - TOTAL OUT	+4530	+1280	+900	-2390	-480	-280	-2110	-720	-40	+690
BLOOD										
SERUM CHLORIDE M. EQ. PER LITER		107.5		115.2			105.9			

one patient with low drainage, while in the other the balances were not so good, due to smaller intake and periods of gastric distention with vomiting. In one of the cases with high jejunal suction drainage the patient cooperated so well in alimentation that he might well have been carried with little or no parenteral fluids.

During the early period of intubation, before the distention is controlled, parenteral fluids are imperative, since the patient not only is hardly likely to absorb fluid, but loses excessive fluids and salt from the gastro-intestinal tract. These studies were not made until decompression was effected and, therefore, do not indicate the losses from the intestinal tract during distention. Since the quantity of drainage from the high jejunum is frequently lower than the intake, it is obvious that aspiration is not complete, and that fair quantities pass the tube tip and are absorbed lower down. Even if we could assume that no fluid passed below the suction tip and that, therefore, the small stretch of jejunum and duodenum above the tube could absorb the quantities indicated by the difference in oral intake and drainage, we would have to account for the absorption of a much greater amount to allow for the secretion of gastric juice, bile, succus entericus, and pancreatic juice. We are, therefore, forced to the logical conclusion that even when suction drainage is effective constantly all material passing the tip is not aspirated. It is fortunate that gas is more easily aspirated than fluid. It is logical that this simple physical fact allows removal of practically all gas with a moderate amount of fluid passing the tube tip.

For purposes of brevity we are presenting one case in detail with data collected over a nine-day period. This case was the best of our series so far as balance studies were concerned during his preoperative period. He was an exceedingly cooperative patient and took fluids and food well, and we present these data to illustrate the possibility of maintaining balances without intravenous saline. It is not our custom to rely solely on oral feedings, nor, except in unusual cases, do we feel that it is good policy. We feel certain, however, that when possible, oral feedings are advantageous in that they decrease the amount of intravenous fluids necessary and offer a better means of controlling the patient.

Table I illustrates the fluid balance on this patient. It is evident that sufficient fluids were absorbed from the gastro-intestinal tract to keep the patient well hydrated and to supply more than enough fluid to excrete a large volume of urine. The drainage from the tube was minimal, and the difference between tube drainage and intake was more than is usually necessary for the average patient. The deficit between intake and output we have assumed to be insensible loss since during this period there was no evidence of retained fluid. Facilities were not available for weighing the patient accurately, so that we have no means of determining weight changes.

Table II illustrates chloride intake and output. The chloride received by vein was administered as whole blood, and the patient received no other intravenous fluid. The daily oral intake of chloride was quite sufficient to

# NUTRITIONAL BALANCE WITH SUCTION DRAINAGE

TABLE III  
NITROGEN BALANCE STUDIES OF J. K. FOR NINE-DAY PERIOD

J. K. - NITROGEN

DATE	16-17	17-18	18-19	19-20	20-21	21-22	22-23	23-24	24-25	TOTALS
INTAKE										
BY VEIN	0.1	0	0	0.1	0	0	0	0	0	0.2
BY MOUTH	6.9	10.8	11.3	11.6	10.3	10.8	12.2	9.4	8.6	91.9
OUTPUT										
BY TUBE	1.4	1.2	1.1	1.9	1.6	1.6	1.6	0.6	0.5	11.7
BY FECES	0	0	0	0.7	0	0.2	0	0	0	0.9
BY URINE	5.3	10.1	10.3	9.5	8.6	8.7	10.4	8.5	8.2	79.6
BALANCE										
ORAL IN - SUCTION	5.5	9.6	10.2	9.7	8.7	9.0	10.6	8.8	8.1	80.2
TOTAL INTAKE	7.0	10.8	11.3	11.7	10.3	10.8	12.2	9.4	8.6	92.1
TOTAL OUTPUT	6.7	11.3	11.4	12.1	10.2	10.7	12.0	9.1	8.7	92.2
TOTAL IN - TOTAL OUT	+0.3	-0.5	-0.1	-0.4	+0.1	+0.1	+0.2	+0.3	-0.1	-0.1
BLOOD										
N. P. N. MGMS. PER 100cc		29.3		27.6			25.7			
UREA N. MGMS. PER 100cc		23.4		22.3			19.6			

TABLE IV  
SODIUM BALANCE STUDIES OF J. K. FOR NINE-DAY PERIOD

J. K. - SODIUM

DATE	16-17	17-18	18-19	19-20	20-21	21-22	22-23	23-24	24-25	TOTALS
INTAKE										
BY VEIN	1000	0	0	1000	0	0	0	0	0	2000
BY MOUTH	5490	5180	2860	2340	2550	4130	3120	2180	2200	30050
OUTPUT										
BY TUBE	1580	1450	345	2040	540	1980	670	551	576	9732
BY FECES	0	0	0	327	0	65	0	0	0	392
BY URINE	695	1120	2040	3020	2390	2520	3670	2340	1800	19595
BALANCE										
ORAL IN - SUCTION	3910	3730	2515	300	2010	2150	2450	1629	1624	20318
TOTAL INTAKE	6490	5180	2860	3340	2550	4130	3120	2180	2200	32050
TOTAL OUTPUT	2275	2570	2385	5367	2930	4565	4340	2891	2376	29719
TOTAL IN - TOTAL OUT	+4215	+2610	+475	-2047	-380	-435	-1220	-711	-176	+2331
BLOOD										
SERUM SODIUM M. EQ. PER LITER		147		149			154			



supply his requirements and was in excess of that lost by suction. During the entire nine-day period the total output of chloride was within 0.7 Gm. of the total intake and the chloride concentration in the blood was maintained at a satisfactory level.

Sodium and potassium balances, as shown in Tables III and IV, reveal that so far as these two substances are concerned the balances are fairly well maintained on oral intake. Serum sodium levels were maintained (Table IV). The serum potassium level is of less importance and the decrease shown here is of no significance.

Of great interest are the data shown in Table V, which indicate that this

TABLE V  
POTASSIUM BALANCE STUDIES OF J. K. FOR NINE-DAY PERIOD  
J.K. - POTASSIUM

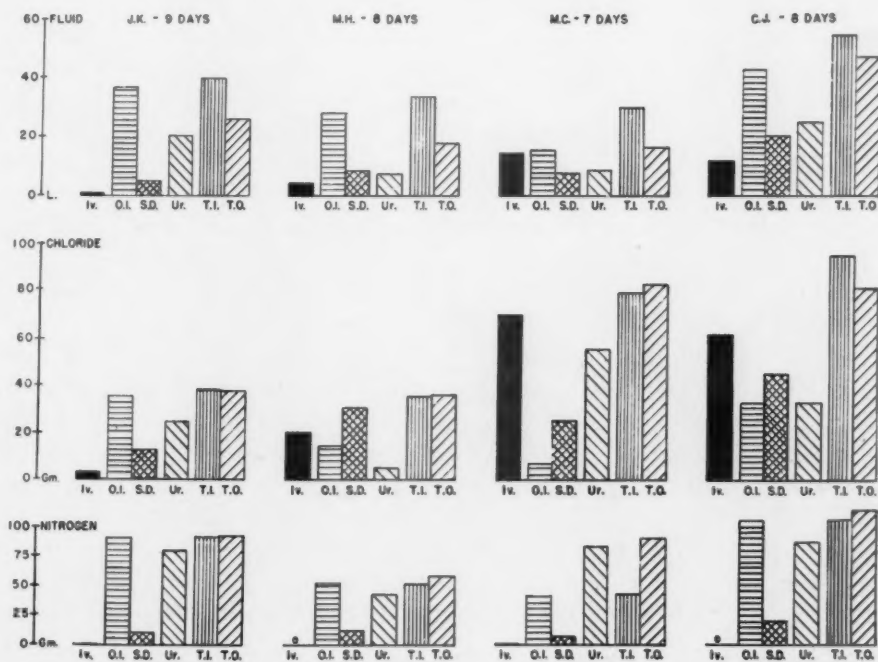
DATE	16-17	17-18	18-19	19-20	20-21	21-22	22-23	23-24	24-25	TOTALS
INTAKE										
BY VEIN	1000	0	0	1000	0	0	0	0	0	2000
BY MOUTH	750	940	1200	1000	1360	1340	1350	1070	1220	10230
OUTPUT										
BY TUBE	120	200	74	165	70	650	81	47	62	1469
BY FECES	0	0	0	380	0	80	0	0	0	460
BY URINE	810	860	1180	990	1160	1280	1570	1550	1000	10400
BALANCE										
ORAL IN - SUCTION	630	740	1126	835	1290	690	1269	1023	1158	8761
TOTAL INTAKE	1750	940	1200	2000	1360	1340	1350	1070	1220	12230
TOTAL OUTPUT	930	1060	1254	1535	1230	2010	1651	1597	1062	12329
TOTAL IN - TOTAL OUT	+820	-120	-54	+465	+130	-670	-301	-527	+158	-99
BLOOD SERUM POTASSIUM MGMS. PER 100 cc.		20.7		16.2			13.7			

patient has been kept in fair nutritional state so far as protein utilization is concerned. The amounts of nitrogen lost in the suction drainage are small as compared with the intake. The urinary nitrogen excretion, of which approximately 80 per cent was urea, is quite satisfactory, and with the total intake and total output of nitrogen over the nine-day period being about equal, indicates that he has utilized sufficient protein to replenish body losses of protein.

A composite graph representing the data on all four of the patients regarding balance studies of fluid, chloride, and nitrogen is presented in Graph 1. The data on J. K. are represented graphically for comparison with those from other patients. The oral intake in excess of losses by suction drainage is strikingly larger than in any of the other patients. The other patient with

drainage from the ileum (M. H.), whose oral fluid intake-output difference ought to have been sufficient to maintain fluid balance, appeared slightly dehydrated regularly, and the urine volume was quite low. Intravenous sodium chloride was given this man and it is interesting to note that his chloride balance was good. He lost a large amount of chloride in his drainage and sufficient chloride was given by vein to correct this. However, despite the fact that the total intake of chloride was almost as great as the total output, the excretion in the urine was quite small, and this man could

INTAKE - OUTPUT SUMMARY



GRAPH I.—Composite graph showing fluid, chloride, and nitrogen balances in four patients studied.

have had more intravenous salt as well as glucose solution with advantage. The reason for his low intake of chloride was that he took food poorly and his intake consisted in large part of water and on several occasions the patient vomited because his stomach dilated after aerophagia. This also accounts for his low protein utilization which resulted in a negative nitrogen balance, which indicated that he was not well maintained nutritionally despite the fact that the tube was in the lower ileum. In addition, the low daily excretion of nitrogen attests to the fact that we were not able to maintain nutrition. However, the amount of protein which he did utilize from his oral intake was of definite advantage in that it did provide him with some protein which he would not have had without oral feeding.

In regard to the two patients (M. C. and C. J.) with high jejunal drain-

age, the high level might suggest that oral intake would be of little consequence in maintaining the patient in fluid and nutritional balance. That this was to some extent our concept is illustrated by the fact that large quantities of intravenous fluids were administered. Either of these patients might have been maintained on smaller quantities of intravenous fluids to some advantage. In both these cases with jejunal suction about half their fluid intake was aspirated. C. J. had a much greater intake of fluid than M. C. and accordingly absorbed more fluid from his intestinal tract. The urine output on M. C. was well over a liter daily, and C. J. excreted excessively large amounts of urine, averaging almost 3,000 cc. daily. The difference between total intake and output, which might be assumed in both instances to be insensible loss, was much less in C. J. than in M. C. Since the serum protein level of C. J. was 8.3 at the beginning of the study and dropped to 7.1 shortly after, it might be assumed that this was the result of replacing fluids lost during dehydration. However, the serum chloride was not abnormal. In both M. C. and C. J. the amount of chloride lost in suction was greater than that taken by mouth, and despite the low urine volume of M. C. her chloride excretion was quite large. Since M. C. was a female and urine and feces were grouped together, this might be suspected of accounting for the high value for urinary chlorides. Fecal studies on other patients indicate that this was not so, but that the urine was more concentrated. Both these patients received more intravenous saline than should have been given, and while they were capable of excreting large amounts of chloride, it would have been better had we given a portion of the intravenous fluid as glucose in water. It is to be noted that while M. C. excreted slightly more chloride than she ingested, C. J. actually retained chloride despite the fact that there was no noticeable edema. A portion of this might be accounted for in retained feces since no attempt was made to clean the lower bowel at the beginning and end of the study. Nitrogen balance was not maintained in either of the patients with jejunal suction. This was to be expected in M. C., whose protein intake was not great, and the patient had a moderate amount of fever for a few days. In C. J., however, the difference between intake and suction drainage was adequate and a better balance should have resulted. We are at a loss to explain the poor balances on C. J. but we feel fairly certain that these were not due to the most obvious possible fault, that of measuring, since the discrepancies are not always in the same direction.

These data indicate that in patients with low ileal drainage it is possible to maintain good fluid, salt, and nutritional balance if the patient ingests a sufficiently larger quantity of food, salt, and fluid than is removed by suction. However, even in cases with drainage from the lower ileum this should not be relied upon entirely. When suction is exerted at higher levels it is much more difficult if not impossible to maintain good balances, especially as regards salt. The amount of material which can be absorbed by the gastrointestinal tract in cases decompressed by suction drainage is of decided

advantage in maintaining the patient in good fluid, salt, and nutritional balance. The use of parenteral fluids in conjunction with oral intake in excess of suction drainage is important.

We recognize that with variations in the amount of suction drainage from patient to patient, four patients are not sufficient to draw broad conclusions concerning balances. We are, therefore, presenting this material as a preliminary report and are continuing this study.

We wish to thank Dr. Charles G. Johnston, Professor of Surgery at Wayne University, under whose direction this study was carried out, for cooperation and guidance.

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DISCUSSION.—DR. WALTMAN WALTERS (Rochester, Minn.): When, a few weeks ago, I discussed with my colleague, Doctor Snell, the possibilities of contributing to this very excellent group of papers, he said that if I expected in five minutes to contribute anything to what a high-pressure biochemist like John Peters had a chance to say in 20 minutes, I was crazier than he thought I was. So my discussion is really going to revolve around a discussion of some of the clinical aspects of dehydration toxemia rather than physiologic chemical studies in such cases.

I thought that Doctor Peters in his presentation of his charts, particularly that first one, very clearly showed that there are clinical evidences of dehydration toxemia, which sometimes occur before the chemical changes become marked, and I refer particularly to the evidence of the decrease in urinary output in cases with dehydration toxemia.

It seems that the interesting thing, also, in such cases is that one sees the red cheeks of such patients due to the alkalosis, the dry skin and tongue, and in addition the blood pressure usually is found to be below normal. I think it is worth while to call attention to these clinical evidences of dehydration toxemia, because in many instances the cooperation of men skilled in biochemical tests is not available and if, therefore, one recognizes the possibility of dehydration, it can be compensated for.

I was very much interested in what Doctor Maddock had to say regarding the administration of too much salt solution and the development of edema which occurred as a result. One sees that, fortunately, infrequently. If one does not administer a total of more than 1,000 cc. of normal saline above the amount of fluid excreted, regardless of whether the patient has an obstructing lesion of the gastro-intestinal tract or biliary tract or a fistula, in other words if a positive fluid balance of 1,000 cc. is maintained, that 1,000 cc. being administered as normal saline, the patient usually does not experience edema that is due to chloride retention.

On the other hand, there is equal danger in administering hypertonic solu-

tions of glucose to patients to whom one does not want to administer too much salt, and, as Doctor Peters emphasized in his discussion, that water and food given orally in the presence of gastro-intestinal obstruction will frequently cause a depletion of chlorides; similarly hypertonic glucose solution intravenously injected will produce in some cases depletion of chloride when injected too frequently, especially if a biliary fistula is present. I recall such a case. A man, who had obstruction of the common bile duct as the result of a stone, was given glucose because of diabetes but in too large a concentration, and although insulin was given to metabolize the glucose, a depletion of chlorides developed. The clinical evidence of this condition was rather marked owing to the incoherent remarks which the patient would make in discussing his progress. Also, the blood showed a decrease in the chloride.

In the symposium, no reference has been made to the physiochemical changes which occur as a result of the loss of fluids and electrolytes through biliary and intestinal fistulae. I recall a case of external biliary fistula in which a tremendous amount of bile was lost on the seventh and eighth days following operation, with a low urinary output which you will recall I mentioned as clinical evidence of dehydration. A tremendous amount of total chloride was lost in the bile, more than six times the normal, and there was a marked reduction of the urinary base. With the administration of 22 Gm. of sodium chloride and 20 Gm. of sodium lactate daily for six days, there was a normal excretion of base in urine and bile and a decrease in the excretion of sodium chloride in urine and bile to normal limits and, coincidentally, a tremendous decrease in the amount of bile excreted externally (Table I).

TABLE I  
CHLORRHEA: LOSS OF BASE AND CHLORIDE

Days Postopera- tively	Output, Cc.		Chloride, Gm.		Base	
	Bile	Urine	Urine	Bile	Urine*	Bile*
7 and 8	6,710	810	0.38	50.2	0.4	9.4
9	4,000	1,070	1.9	28.9	0.7	5.6
9 to 15	22 Gm. of sodium chloride and 20 Gm. of sodium lactate were given daily					
13	1,070	2,090			2.3	1.5
14	1,130	1,830	7.2	8.1	2.4	1.5

\*As liters of tenth normal base.

Whether or not this was due to the administration of chloride is debatable, in view of the marked reduction in the external drainage of bile which probably was the most important factor concerned. This, I think, is of particular importance, because if one keeps track of the fluid obtained through suction apparatus or lost in vomitus and in the urine, one frequently has a good indication of progress, provided that a 1,000 cc. positive fluid balance is obtained.

Another way of supplying the necessary fluids and electrolytes to patients who experience postoperative obstructions, particularly those in connection with gastro-intestinal anastomosis, is by the performance of jejunostomy. In one case which I recall, a tremendous loss of fluid occurred as a result of obstruction at the gastrojejunal stoma following a Pólya-type of resection. An elevation of the blood urea and a drop in the blood chloride occurred. By the performance of jejunostomy, under local anesthesia, although the excre-



tion of fluid by the stomach continued high, physiochemical balance was kept under control for food, electrolytes and fluid could be administered through the jejunostomy tube until the site of anastomosis opened. About three years ago I reported seven cases of this type, in which the inflammation subsided in periods ranging from 28 to 36 days with gastro-intestinal continuity carrying on satisfactorily.

I recall another case of a similar type, in which obstruction occurred following gastrojejunostomy for duodenal ulcer. There was a characteristic rise of the concentration of blood urea and a fall in the blood chlorides as a result of the loss of fluids by vomiting. With jejunostomy, physiochemical balance was maintained and the lumen at the site of gastrojejunostomy opened on the fortieth day. It has been our experience, too, in cases of this type that sometimes when large amounts of fluid such as glucose are injected intravenously they may be excreted into the stomach, and I believe that occasionally I have smelt the glucose in the gastric secretion when the fluid was excreted that way.

I think that this symposium has been an excellent one. I do think that we must not overlook the clinical factors in estimating progress in these cases. I believe that sometimes we give too much fluid in such cases and that a positive fluid balance of 1,000 cc. is usually adequate.

DR. OWEN H. WANGENSTEEN (Minneapolis, Minn.): This has been a most interesting and profitable discussion, I am sure, for all of us. I am pleased to note that into this discussion have come reservations concerning overdeluging the patient with fluid, as well as references to thwarting dehydration and dechlorination. All of us who deal with the practical aspects of these problems on the wards may fall into both types of error.

The work of Collier and Maddock, and their associates, on the fluid requirements of patients has focused the eyes of surgeons on the great importance of adequate orientation in these particulars. The paper by Doctor Peters, I think, is of great practical importance to the surgeon and we shall all look forward to the opportunity of studying it when it appears in print. Quite properly, Doctor Peters placed considerable emphasis on the matter of distention as related to the absorption of fluid and to the prophylaxis of distention after abdominal operations. He referred to the work of one of my associates, Dr. Clarence Dennis, who demonstrated that the placement of water on the exposed ileum of the dog may cause ulceration of the mucosa. Dennis, however, was unable to produce similar changes by the placement of water on the gastric mucosa of the dog. Doctor Peters' suggestions concerning the oral administration of water to postoperative surgical patients are interesting. It may be that the oral administration of saline solution is preferable. However, I find it difficult to get patients after operation to ingest more than half a liter of saline solution unless the salt is given in capsules. Patients do enjoy the refreshment of cool water.

With reference to Doctor Peters' remarks upon the prophylaxis of distention, I would like to point out that, together with Dr. Charles Rea of my department, it was observed that the swallowed air factor was a most significant item in the establishment of intestinal distention (*Surgery*, 5, 327, 1939). In dogs, with transection of the cervical esophagus, the proximal end opening at the skin, the distal end being closed, it was found that such dogs tolerated complete ileal obstruction unusually well. One such dog survived for 57 days, dying ultimately of starvation. There was no distention at autopsy. The swallowed air factor having been excluded by esophagostomy, the bowel was able to reabsorb the secretions dumped into the intestinal

canal—namely, gastric juice, bile, pancreatic juice and succus entericus. When, however, the distal end of the esophagus in the neck was left open, the dog aspirated air into his stomach, the intestine dilated with the establishment of ileal obstruction, and the animal did not survive the distention long. This occurrence emphasizes the great importance of prophylaxis of intestinal distention described by Doctor Peters.

Most of the discussion in this symposium has hedged about the item of control of the patient throughout the operative period. I might, therefore, say something about the matter of the early care of the patient after operation. A common error among surgeons is failure to fully appreciate the profound effect of severe operation and prolonged anesthesia upon the loss of fluid by sweating. Anesthesia, whether local, regional or general, causes a dilatation of the capillaries of the skin with consequent loss of large amounts of fluid. The salt content of this fluid averages probably about 3 Gm. per liter. The oliguria which patients present the day following operation, not infrequently finds its explanation in the failure on the part of the surgeon to reckon adequately with the loss of fluid through this source. Whereas there are satisfactory means of determining whether patients are adequately chlorinated the most practical of available means of knowing whether a patient is hydrated adequately are the absence or presence of thirst and a satisfactory output of urine. Overchlorination of patients is frequently responsible for oliguria. I have come to feel that the loss of fluid through perspiration is so important that our nurses on surgical floors try to compute roughly the fluid loss through this source in items of 1, 2, 3 or 4 plus. For a patient who has had a protracted operation under anesthesia, and who has not lost large quantities of fluid from the gastro-intestinal canal, 5 Gm. of sodium chloride and 3,000 to 4,000 cc. of fluid will usually suffice, and insure a satisfactory urine output, during the first 24-hour period.

In patients in the older age-group (over 60), we have returned largely to the subcutaneous route of administering fluid. It has been shown, even in young sturdy patients with good cardiac reserve, that intravenous injection of fluid at the rate of 15 cc. per minute will accelerate the heart rate. Patients with malignancies in the upper age-brackets not uncommonly have coronary sclerosis with diminished cardiac reserve. Intravenous administration of fluid to such patients not uncommonly elicits cardiac pain and may provoke pulmonary edema. I have come to insist on the subcutaneous administration of fluid to such patients and find it eminently satisfactory.

A number of my associates and I have been interested in the matter of attempts at maintaining patients with obstruction in the upper digestive tract in nitrogen equilibrium. Up until now, surgeons have concerned themselves solely with the item of proper water and electrolyte balance and the administration of enough glucose to prevent ketosis. Why not also, maintenance of patients in proper caloric and nitrogen balance?

Our plan in patients presenting obstructions (cancer or ulcer) at the gastric outlet is to avoid jejunostomy or preliminary gastrojejunostomy. Such a patient may be maintained in satisfactory water, electrolyte, caloric and nitrogen balance, and operated upon after satisfactory preparation, as though he were not obstructed. Five hundred cubic centimeters of human plasma daily usually suffices to maintain nitrogen equilibrium. A similar amount of whole blood will not maintain a patient in positive nitrogen balance. Recent experience with the intravenous administration of amino-acids (F. Stearns & Co., Detroit) suggests that this is a simple and practical manner in which to supply patients with a source of nitrogen when the gastro-intestinal canal is not available for feeding. I like to have patients who can not take protein by

mouth get about 40 grams of protein intravenously. Satisfaction of fluid, glucose and mineral requirements is not enough. Clinical trial shows that patients with a deranged gastro-intestinal canal do better when the patient is maintained in nitrogen equilibrium as well.

During the past year, we have been probing the feasibility of administering bovine plasma to man intravenously. In a preliminary communication on the subject (*Proc. Soc. Exper. Biol. and Med.*, **43**, 616-621, 1940), it has been indicated that bovine plasma may be given to man in fairly large quantities. We observed that bovine plasma so administered was retained and was not excreted in the urine; it is our impression that it is retained and metabolized. The largest amount that has been given any single patient is 1,500 cc. Our observations to date are not numerous, but more than 50 patients have received bovine plasma in quantities of 100 cc. or more intravenously. There have, of course, been some reactions. We have had only one anaphylactoid reaction, in an asthmatic. There have been no deaths. Much remains to be done to establish the practicability of the method for general clinical use. My surgical associates and I are hopeful that the method may become useful in the treatment of shock and contracted protein stores in man, both in civil and war surgery. It is not unlikely that separation of the albumin and globulin fractions may pyramid the usefulness of the method, for the globulin fraction appears to be the more toxic. However, to date, we have had more success (less reactions) with the administration of whole bovine plasma than with albumin fractions alone. Surgeons must give more thought to the matter of maintenance of nitrogen equilibrium in obstructed as well as debilitated patients.

DR. JOHN P. PETERS (New Haven, Conn., closing): It is only when I am among surgeons or physicians that I am ever flattered by being called a high-powered chemist. Chemists know me. I mention this because I did not mean to neglect emphasis on the clinical aspects of these cases, although I know I was a little hasty to get over to the chemical side. I mentioned, especially in my last words, that you need not worry much about the patient who is excreting 1,000 to 1,500 cc. of urine or more a day. I think if more attention were given to this we would not have to do quite so much blood chemistry, and often make so many mistakes in giving fluids.

Now I want to speak a moment about this business of excessive chloride. I agree that one should not give enormous amounts of chlorides and that often a great deal too much is given. I think it is a mistake, also, to give this chloride in many instances intravenously, especially in the light of Doctor Blalock's studies, in which he shows that, in this way, in patients with shock you can wash protein out of the blood. My own practice is to administer saline chiefly under the skin, as Doctor Wangenstein has suggested, and to reserve the vein for hypertonic glucose, if it is necessary. I say hypertonic. I prefer to use 10 per cent to get it into a small volume, and I give that intravenously because glucose under the skin is irritating and withdraws fluid from the blood stream, at least temporarily.

Doctor Maddock spoke, in his cautions, of edema occurring with hypochloremia, or low chlorides. I think that this is quite common. I am not sure that the presence of the hypochloremia itself may not bring about such disorganization of the body as to provoke the edema. In many of these cases, one need not encounter all the difficulties that Doctor Maddock has spoken of if small amounts of hypertonic saline are given to overcome the salt deficiency in the plasma and bring the osmotic pressure of the plasma

up to normal. We give 2 per cent saline in relatively smaller volumes than we would normal saline to these cases, sometimes with very good results.

I believe that attention to the electrolyte pattern and administration of salt according to the disturbances in this pattern, with due regard to the presence of edema and excessive hydration when it occurs, may obviate these difficulties and better the care of the patients.

DR. JOHN SCUDDER (New York, N. Y., closing): I should like to ask a question. Has Doctor Peters ever seen a case passing two or three liters of urine and yet dehydrated? When the total ionic content of the blood is decreased in Asiatic cholera, and a severe case of intestinal obstruction, and you give a physiologic salt solution, you have not enough base to retain that fluid and the person puts it out. Have you seen that type of case in severe burns? We have had cases passing 2 or 3 liters of fluid, but yet if you make studies of their blood it will be found to be concentrated. If you determine the salt content, you will find that their total base is decreased. Gamble has brought up the question that you cannot retain water unless you have sufficient base. In cases of base depletion will you not have an excess of urine output if you do not administer enough base?

DR. JOHN P. PETERS (New Haven, Conn., closing): You are more likely to have it in these cases than you are in patients with gastro-intestinal disturbances, of which I especially spoke. I, perhaps, should speak a moment here about the problem of burns and infections. It is quite well recognized that in pneumonia and certain pulmonary diseases and other highly febrile conditions, there is a tendency for individuals to keep the concentration of base continually low in the serum. Under those circumstances they will dehydrate themselves because they will waste salt if you do not give it to them. On the other hand, if you give excessive salt in the presence of conditions of this kind, you are not always able to restore the salt concentration in the serum to normal, even if you push it to the point of giving these patients edema. The mechanism of this is not clear yet; but in pneumonia there is a tendency to waste salt in the urine and to waste fluid with it, and to maintain a relatively low concentration in the serum. This may have a particular bearing on the problem of burns.

DR. WALTER G. MADDOCK (Ann Arbor, Mich., closing): I should like to emphasize, further, a difference in the response of surgical patients, depending upon their general condition, to the administration of sodium chloride solutions given according to our "clinical rule" to correct electrolyte deficiencies. The patients who have had a recent or acute loss of electrolytes, such as would occur from vomiting due to an incarcerated hernia, and whose general nutrition is good, usually, after their operation and saline solution administration, have a prompt return of their plasma electrolytes to normal.

The second group are the patients who have a chronic illness producing malnutrition or who have the other conditions of the sick surgical patient such as sepsis, significant renal and hepatic damage or severe acute or chronic hemorrhage. When given calculated amounts of saline solution to correct an electrolyte deficiency, the correction for these patients is often incomplete. An occasional one will excrete quite an amount of sodium chloride in the urine, and this loss will account for the failure of the plasma electrolytes to reach normal. The majority, who show only a partial return of their plasma electrolytes to normal, do so, we feel, because more than usual of the saline solution goes to the interstitial spaces. Attempts to raise the plasma electro-



lytes by giving more salt have simply resulted in more weight gain, so we have abandoned this attack. We feel that the first administration of salt by the "clinical rule" provides sufficient electrolytes for correction of the deficit, and it has been our experience that if the patient's general condition improves, if he begins to eat, then the excretion of water and sodium chloride in the urine increases, there is some loss in weight, and the plasma electrolytes come up to the normal level.

For the vast majority of general surgical patients the handling of the electrolyte problem by the "clinical rule" for restoration and the "volume-for-volume" replacement for maintenance has been a working procedure in the hands of our resident staff without the frequent use of expensive chemical studies.

DR. R. MAYO TENERY (Detroit, Mich., closing): Doctor Peters mentioned that patients with gastro-intestinal suction do better if he gives them either nothing by mouth or only normal saline by tube. We believe that it is better to give food to patients with long tube suction, as they are then much happier and nutrition can be kept up very well.

Graph 1 shows that an appreciable amount of dietary nitrogen was absorbed and utilized by all four patients. M. J. did not absorb enough to keep up a good balance, but she was better off than if she had been given no nitrogen by mouth.

Our long-tube diet consists of almost any food except that having a high fiber content. When the tube is in the lower ileum, patients can keep up good nutrition if they take an adequate diet, and very few of them need much in the way of intravenous fluids. Of the two patients with upper jejunal suction, each had a negative chloride balance, as far as their oral intake compared to suction drainage was concerned; but they did take in more nitrogen and water than was removed by tube.

Thus, we feel that food makes our patients more comfortable and maintains their nutrition much better than if they were given nothing by mouth.



## A CLINICAL STUDY OF THE PLASMA VOLUME IN ACUTE INTESTINAL OBSTRUCTION\*

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IN EXPERIMENTS on animals with uncomplicated obstruction of the small intestine a fall in the volume of circulating plasma sufficient to account for the death has been observed.<sup>1</sup> The evidence is clear that this loss of plasma may occur in the absence of dehydration or the accumulation of significant quantities of fluid in the cavity or wall of the intestine or in the peritoneal cavity.<sup>2</sup> Moreover, the intravenous administration of large amounts of fluid and electrolytes does not prevent the decrease in plasma volume, whereas the intravenous injection of an equal or smaller volume of plasma not only maintains the plasma volume but prolongs the life of the animal.<sup>3</sup> Decompression, as might be expected, halts the loss of plasma and may even permit substantial recovery of the fraction lost.<sup>4</sup> Desoxycorticosterone acetate also prevents the plasma loss, if given early, and may increase the volume above normal.<sup>5</sup> Finally, distention of the colon and of the gallbladder does not cause a significant plasma loss while distention of as little as two feet of small intestine may do so.<sup>6</sup>

The purpose of this communication is to present clinical evidence confirming some of these experimental findings.

**Case 1.**—A 40-year-old man with an indirect inguinal hernia, but otherwise in good health, was subjected to a repair of the hernia. After two uneventful postoperative days he gradually became distended. Enemata were ineffectual. Periumbilical colic and vomiting followed. Gastric lavage was necessary. When the abdomen was much distended and tense, a roentgenogram showed many distended loops of small intestine (Fig. 1). At this time the plasma volume was 2,414 cc.† Thirty-six hours after the introduction of a Miller-Abbott tube the distention largely disappeared and the plasma volume rose to 3,408 cc., an increase of 994 cc.

**COMMENT.**—This is presumably an instance of transitory mechanical rather than functional ileus. If the plasma volume after decompression is regarded as the normal for this patient, it is apparent that intestinal obstruction resulted in a loss of plasma of 30 per cent. It is significant that this loss of plasma occurred in spite of the administration of large amounts of fluid; it was corrected only by decompression.

\* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

† All plasma volumes were measured by the method of Gibson and Evelyn<sup>7</sup> on admission or at least several, and usually, about 12 hours after parenteral fluids were stopped, so that very little of the recorded volumes can be regarded as due to hydremic plethora.

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**Case 2.**—A woman, age 78, entered the hospital with nausea, vomiting and obstipation of four to five days' duration. On admission she was found to have auricular fibrillation and a markedly distended, tense abdomen with visible peristalsis. A roentgenogram of the abdomen showed extreme gaseous distention of loops of small intestine and a calcified gallstone in the lower ileum (Fig. 2). The plasma volume was 2,020 cc. Because of her precarious condition nonoperative decompression by the Miller-Abbott tube was attempted, but without success owing to her refusal to cooperate. One hundred per cent oxygen inhalation was then tried, again without success for the same reason. Eight hours after admission the plasma volume had fallen to 1,661 cc. Surgical intervention followed immediately. The gallstone was removed and an enterostomy tube was inserted. Eighteen hours later abdominal distention had decreased considerably, and the plasma volume was 2,562 cc., an increase above the previous measurement of 900 cc. A roentgenogram two



FIG. 1.—Case 1: Transitory postoperative mechanical obstruction of 36-48 hours' duration. Moderate distention. Plasma loss 29 per cent. Plasma gain after decompression 41 per cent.



FIG. 2.—Case 2: Gallstone obstruction of ileum of four days' duration. Extreme distention. Plasma loss 45.5 per cent. Plasma gain after decompression 83.5 per cent. Arrow points to gallstone.

days later, however, still showed some loops distended with gas. On the fifth postoperative day the plasma volume had risen to 3,048 cc. A roentgenogram on the sixth postoperative day showed almost complete deflation.

**COMMENT.**—The very low plasma volume observed just before operation and the final increase of 83.5 per cent following effective decompression are in conformity with the experimental finding that the plasma volume falls during distention and rises following decompression.

**Case 3.**—A 29-year-old male was operated upon for recurrent right lower quadrant pain, nausea and vomiting of several months' duration. Several loops of ileum were found adherent to one another by numerous adhesions, which were divided. Nausea and vomiting recurred a week later and again two weeks later. On this last occasion food and fluids by mouth could not be retained; constipation was complete and distention appeared. A roentgenogram showed many distended loops of small bowel containing fluid

levels. The plasma volume was 2,494 cc. Four days later, after effective decompressive procedures, the plasma volume was 3,339 cc., a gain of 34 per cent above the previous measurement.

**COMMENT.**—The magnitude of the plasma volume change in this patient was less than in the two preceding patients, perhaps because the degree of gaseous distention was less marked.

If it is true that the general physiologic disturbances in uncomplicated intestinal obstruction are due to the resulting distention rather than to the obstruction *per se*, one should expect to find the same constitutional changes when severe distention of nonobstructive origin is present. In support of this inference we present the following case:

**Case 4.**—An obese female, age 42, was operated upon for a large papillary cystadenocarcinoma of the left ovary. She was immediately placed on one of a group of postoperative diets which are being studied to evaluate the distending capacity of different types of foods. On the first postoperative day the abdomen became tense, distended and tympanitic. The following day the distention was extreme, nausea and vomiting occurred and nothing could be passed by rectum, even with the aid of repeated enemata. The plasma volume was 2,531 cc. By the use of an intragastric tube, hot stupes, more enemata and a change in diet to what we believe are nondistending foods, complete deflation resulted, after the subsequent three days. On the sixth postoperative day the plasma volume rose to 4,221 cc.

**COMMENT.**—If this final measurement be taken to represent this patient's normal plasma volume, the distention may be considered to have caused a 40 per cent loss in circulating plasma; or, stated the other way, the decompression caused a gain of 67 per cent in circulating plasma. This is indirectly reflected in the accompanying change of 21 per cent in the hematocrit (Table I—Case 4).

A similar, though less striking, observation was made in the following case:

**Case 5.**—A 65-year-old man became increasingly distended following suprapubic cystotomy and bilateral vasectomy for obstructing prostatic hypertrophy. On the fourth postoperative day the abdomen was enormously distended and tympanitic, audible peristalsis was absent and a roentgenogram showed marked gaseous dilatation of the small intestine. The plasma volume was 2,868 cc. Following the institution of gastric suction, 100 per cent oxygen inhalation, enemata and heat to the abdomen for 24 hours, the distention decreased. On the following day after an effective bowel evacuation the distention disappeared. Four days later the plasma volume was 3,725 cc., which represents a gain of 29 per cent.

**COMMENT.**—Since the disturbance in this and in the previous instance was clearly one of adynamic ileus, it is apparent that the plasma loss in ileus, whether of mechanical or functional origin, is due to the distention common to both. In the light of this observation, severe distention, even of functional origin, may become a vital matter.

The degree of dilatation of distended loops as seen roentgenologically or as suggested by the increase in size of the abdomen does not necessarily indicate the degree of intra-intestinal pressure, which is responsible for the loss of plasma. Such objective signs may, therefore, not always be relied upon as a

guide to the extent to which plasma is being lost. Consequently, even when the roentgenograms of two different patients show comparable degrees of dilatation, the extent of the plasma loss may differ considerably. Thus the roentgenogram in the following patient showed greater gas accumulation in the small intestine than in Case 1. The plasma loss, however, as will be seen below, was less in spite of the longer duration of the obstruction.

**Case 6.**—A 72-year-old woman, with a history of a lower abdominal operation 14 years previously, entered the hospital complaining of intermittent, periumbilical colicky pain, nausea, constipation and increasing distention of four days' duration.



FIG. 3.—Case 6: Mechanical obstruction of ileum of four days' duration. Marked distention. Plasma loss 25 per cent. Plasma gain after decompression 33.8 per cent.



FIG. 4.—Case 7: Strangulation of loop of ileum in femoral hernia, probably of four days' duration. Traces of gas in intestine. Plasma loss 17 per cent. Plasma gain following release of intestine 21.6 per cent.

*Physical Examination* showed marked abdominal distention and tympany on percussion. Roentgenograms of the abdomen showed widespread dilatation of loops of small intestine (Fig. 3). The plasma volume was 2,116 cc. Satisfactory though not complete decompression was achieved during the following 20 hours by the continuous inhalation of 100 per cent oxygen. This was followed by exploratory celiotomy. A string adhesion running from the mesentery of the ileum to the presacral peritoneum was found completely constricting the ileum. The obstruction was released and an enterostomy performed. After complete deflation, on the seventh postoperative day, the plasma volume was 2,832 cc. The loss from distention was therefore only 25.3 per cent, whereas in Case 1, where much less gas seemed to be present, the loss was 29.1 per cent.

**COMMENT.**—The varying clinical course of apparently comparable patients with intestinal obstruction similarly treated may well be ascribable to differences in plasma loss due to differences in intra-intestinal pressure, which de-

TABLE I  
CHANGE IN PLASMA VOLUME, TOTAL BLOOD VOLUME AND HEMATOCRIT, PRODUCED BY INTESTINAL DISTENTION AND DECOMPRESSION

Case No.	Date	Pathology	Change in			Hematocrit	N.P.N. Mg. %	Urine Sp. Gr.	24 hrs.		Remarks
			Plasma Vol. Cc.	Plasma Vol. Per Cent	Red Cell Vol. Cc.				Fluid Intake Cc.	Urine Output Cc.	
1	1/31/40	Small Bowel Obstruction	..	..	..	..	..	..	4,700	1,250	Postoperative mechanical obstruction treated conservatively.
	2/1/40	Distended	2,414	-29.6	2,056	46	25	1.020	2,500	1,000	Gaseous distention of small intestine shown in X-ray
	2/2/40	Decompressed	3,408	+41.1	2,178	39	..	1.018	3,000	1,000	
2	9/22/39:	Small Bowel Obstruction	..	..	..	..	..	..	..	..	Mechanical obstruction due to gallstone in terminal ileum.
	4 P.M.	Distended	2,020*	..	1,587	44	..	..	350	700†	Marked distention of small intestine. Mild secondary anemia. Gallstone removed at operation, 9/22/39
	11:30 P.M.	Distended	1,661	-45.5	1,253	43	..	..	2,900	..	
	9/23/39	Decompressed	2,562	..	1,855	42	..	..	3,600	780	
	9/27/39	Decompressed	3,048	+83.5	1,641	35	26	1.016	1,910	730	
3	1/1/40	Small Bowel Obstruction	2,494*	-25.3	1,494	50	..	1.020	4,200	500	Small bowel obstruction due to right lower quadrant adhesions. X-ray of abdomen, 1/1/40:
	1/5/40	Distended	3,339	+33.8	2,417	42	..	1.018	2,900	1,100	Dilated loops of small bowel in mid- and left epigastrium which show fluid levels. N.P.N. 32 mg. per cent, 1/2/40. Operative decompression
4	10/18/39	Small Bowel Distention	..	..	..	..	..	..	2,000	800	Marked distention produced by diet postoperatively, which responded to conservative treatment. Moderate secondary anemia
	10/19/39	Distended	2,531	-40.0	1,685	40	..	1.016	2,250	700+	
	10/24/39	Decompressed	4,221	+66.7	2,079	33	..	..	2,400	900	



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5	Small Bowel Distention		Adynamic ileus following cystotomy. X-ray showed marked gaseous distention of small intestine. Responded to nonoperative treatment									
	12/23/39											
	12/24/39											
6	Small Bowel Obstruction		Mechanical obstruction due to adherent small intestine in pelvis. X-ray, 2/18/40: Many distended loops of small bowel with fluid levels. Obstruction released at operation. Blood N.P.N. 35 mg. per cent; CO <sub>2</sub> 60 vols. per cent; NaCl 380 mg. per cent, 2/21/40									
	2/18/40											
	2/26/40											
7	Small Bowel Obstruction		Strangulation obstruction of ileum in femoral hernia, with little or no distention									
	10/10/39											
	10/11/39											
8	Small Bowel Obstruction		History of 3 celiotomies, with evidence of mechanical obstruction. Responded promptly to nonoperative therapy. On admission, blood CO <sub>2</sub> 63 vols. per cent; N.P.N. 38 mg. per cent; chlorides 396 mg. per cent									
	12/15/39											
	12/16/39											
9	Large Bowel Obstruction		Obstructive distention of large intestine due to Ca. of sigmoid. Blood chlorides 502 mg. per cent on admission									
	2/7/40											
	2/14/40											

\* These plasma volume determinations were made on admission, before fluids were administered. All other plasma volume determinations were made at least several, and usually 12, hours following the last administration of parenteral fluids.

† These figures do not cover a full 24-hour period.

depends not only on the volume of incarcerated gas but also on the tone of the intestinal musculature and of the musculature of the abdominal wall.

It is nevertheless true, as the following observations will show, that when the volume of incarcerated gas is small or insignificant, the amount of plasma which will be lost in intestinal obstruction is of a relatively low order of magnitude.

**Case 7.**—A 74-year-old male entered the hospital with a history of anorexia, nausea, vomiting and constipation during the preceding three days. A tense, painful mass was found in the right inguinal region. A roentgenogram of the abdomen showed only traces of gas (Fig. 4) in the intestine. The plasma volume was 2,730 cc. At operation soon



FIG. 5.—Case 8: Mechanical obstruction of small intestine of 48 hours' duration. History of two previous celiotomies. Slight distention. Plasma loss 13 per cent. Plasma gain on decompression 15 per cent.



FIG. 6.—Case 9: Obstructing carcinoma of sigmoid of one week's duration. Extreme distention of colon. Slight distention of small intestine. No plasma loss.

after admission a strangulated but viable loop of ileum was released from the sac of a femoral hernia which was repaired. On the following day the plasma volume was 3,320 cc. The loss caused by the obstruction was, therefore, only 17 per cent.

**COMMENT.**—The relatively small change in the plasma volume can be explained by the almost complete absence of intestinal distention.

**Case 8.**—A 58-year-old male, with a past history of two celiotomies, one for a perforated duodenal ulcer, and one for appendicectomy, complained of intermittent periumbilical pain, nausea, profuse vomiting and constipation for 48 hours before entering the hospital.

*Physical Examination* showed a severely dehydrated man with a slightly distended abdomen exhibiting visible peristalsis accompanied by periumbilical, colicky pain. Acute tenderness was present over the scar of the appendicectomy. The urine showed acetone and a specific gravity of 1.026. The blood nonprotein nitrogen was 38 mg. per cent, the

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blood chlorides 396 mg. per cent and the  $\text{CO}_2$  combining power 63 volumes per cent. A roentgenogram of the abdomen showed two or three loops of distended small intestine (Fig. 5). The hematocrit was 46, and the plasma volume 3,112 cc. Gastric suction was instituted, and 100 per cent oxygen inhalation administered. Twenty-four hours later, an enema yielded good results and all symptoms and signs of intestinal obstruction disappeared. On the fourth hospital day the hematocrit was still 46, and the plasma volume 3,591 cc.—a gain on decompression of only 15.4 per cent.

**COMMENT.**—This is an example of well-developed acute obstruction of the small intestine, in which no marked change in plasma volume occurred in spite of the presence of a considerable degree of dehydration. The slight loss of plasma may be accounted for by the fact that there was comparatively little gas and probably no great increase in pressure in the obstructed bowel. The small volume of gas was presumably due to efficient reverse peristalsis, which may achieve the same desirable decompressive results obtained by duodenal suction.

**Case 9.**—A 60-year-old woman entered the hospital complaining of severe lower abdominal pain of 24 hours' duration. She gave a history of complete obstipation for one week and repeated nausea and vomiting of 72 hours' duration.

*Physical Examination* showed marked weight loss, generalized abdominal distention and audible peristalsis. A roentgenogram of the abdomen (Fig. 6) showed extreme distention of the right colon and the proximal two-thirds of the transverse colon and a few dilated loops of small intestine. A barium enema showed obstruction in the sigmoid. The plasma volume was 2,476 cc. An immediate cecostomy was performed. The surgeon noted a very tense, enormously distended cecum and soft distention of the distal ileum. Deflation proceeded rapidly thereafter. A week later, when the general physiologic state was in balance, the plasma volume was 2,494 cc., i.e., substantially unchanged.

**COMMENT.**—The failure to observe any fall in plasma volume in this patient in spite of the extreme degree of distention of at least several days' duration is in accord with our experimental finding that distention of the colon *does not* cause a loss in plasma volume such as occurs after small bowel obstruction.

*Discussion.*—It is evident from the foregoing data that a significant loss of plasma occurs in uncomplicated obstruction of the small intestine only when a substantial degree of gaseous distention (Cases 1, 2, 3 and 6) is present. Since a large loss of plasma also occurs in severe distention of functional origin (Cases 4 and 5), the cause of the plasma loss must be attributed to the distention rather than to the obstruction.

The mechanism by which distention causes the plasma loss is, however, uncertain. One of the ideas current in surgical literature is that distention stimulates the accumulation of the excessive volume of fluid commonly present in the bowel in intestinal obstruction. Even if this be true, though there is substantial evidence to the contrary,<sup>2, 8</sup> the dehydration caused by vomiting and transudation into the intestine can be excluded from responsibility for the major part of the plasma loss for the following reasons: In 13 patients subjected to extreme dehydration in a moist, heated cabinet, by Gibson and Kopp,<sup>9</sup> the plasma loss averaged only 8.7 per cent. The plasma loss in our eight patients with ileus of the small intestine averaged 27.4 per cent. In a normal subject with severe dehydration, Collier and Maddock<sup>10</sup> noted a rise in the nonprotein

nitrogen to 47.5 mg. per cent, while the hematocrit increase was only 7.1 per cent. The increase in hematocrit in those of our patients who showed a marked loss of plasma (Cases 1, 2, 3, 4, 5 and 6) was considerably higher, averaging 19.3 per cent, with a range of 12 to 25.5 per cent.\* Furthermore, none of these patients, as judged by the data on fluid intake, urinary output and specific gravity, gave evidence of an advanced stage of dehydration comparable to that of Collier and Maddock's subject or of Gibson and Kopp's subjects. In Case 1, for example, in which the obstructive distention caused a plasma loss of 29.6 per cent, the fluid intake and output before and during the obstructive phase was entirely adequate and the blood nonprotein nitrogen was 25 mg. per cent; but the hematocrit showed an increase of 15 per cent. This increase in hematocrit must, therefore, have been caused by the loss of plasma which occurred even though the patient was well hydrated. On the other hand, in Case 8, in which dehydration was considerable, indeed, greater than in any of the rest of the group, the plasma loss was only 13 per cent and the hematocrit remained unchanged. *A marked fluctuation in the level of the hematocrit was observed only when marked changes in plasma volume occurred regardless of the amount of dehydration (cf. also Cases 1 to 4 and Case 9, Table I).* For these reasons and for others already stated we do not regard fluid deficit responsible for any substantial portion of the plasma loss in obstructive distention. The prevailing idea that the fulminating character of small bowel distention is to be found primarily in the rapid loss of fluid and electrolytes into the bowel lumen and by vomiting, is untenable in view of the above observations and of the well established fact that adequate replacement of this deficiency accomplishes a necessary but not an immediately vital purpose.

Since the plasma loss cannot be accounted for on the basis of fluid and electrolyte imbalance† or on the basis of effects directly referable to the site of obstruction, we are obliged to assume the existence of some other process as yet undiscovered, which is set in motion by the increase in intra-intestinal pressure.

In pursuit of this objective we proceeded experimentally on the basis that the plasma loss in obstruction of the small intestine might at least in part be due to transudation into the tissues caudal to the compressed intra-abdominal veins. This was suggested by the repeated finding in dogs with distention of the small intestine of a greatly increased femoral venous pressure while the jugular venous pressure remained normal. Further, the institution of pneumoperitoneum at pressure levels of 10–20 cm. of water (20 cm. was used in the small intestine) caused an initial sharp loss of plasma volume, which, however,

\* Since the normal hematocrit varies considerably from one person to another, the initial hematocrit reading, which is likely to be made during the stage of distention, is not useful as an index of the extent of plasma loss unless it happens to be considerably above the average normal value. In this case other conditions causing marked red cell volume changes must be excluded.

† It is pertinent in this connection to recall the observations of Taylor, Weld and Harrison,<sup>11</sup> who produced very low chloride levels in the blood of dogs without noting any of the other disturbances commonly associated with intestinal obstruction.

was generally not fully sustained. But we could not support this etiologic basis for the loss of circulating plasma because negative results were obtained by plethysmographic studies of the lower extremities and by comparative studies of the wet and dry weights of equal amounts of muscle from the upper and lower extremities. In addition, in several experiments utilizing two feet of small intestine, distention at 20 cm. water pressure, which causes no significant degree of abdominal distention, resulted in an extensive loss of plasma. Finally, contradictory evidence appeared in the observation that dogs with distention of the colon at 35 cm. water pressure, which distends the abdomen quite as much as does distention of the small bowel at 20 cm. of water pressure, did not show a fall in plasma volume, and survived more than twice as long as did those with small bowel distention. We therefore concluded that the plasma loss resulting from distention was not due to the simultaneous expansion of the peritoneal cavity or abdominal wall or to pressure on the intra-abdominal veins.

The failure to observe loss of plasma in distention of the colon in dogs was strikingly confirmed in Case 9, in which no loss of plasma occurred in spite of an extreme degree of obstructive distention of the colon, in which the obstruction was of seven days' duration. It is a possible explanation of the clinical fact that patients with obstructive distention of the colon deteriorate less rapidly than do those with obstructive distention of the small intestine.

The clinical observations, herewith reported, confirm our experimental findings in the following respects: (1) That uncomplicated intestinal obstruction causes a serious fall in the volume of circulating plasma; (2) that this fall in plasma volume occurs even when fluid and electrolyte imbalance is prevented; (3) that the plasma loss is not due to the obstruction itself, but to the distention accompanying it and is generally, but not necessarily, proportional to the degree of distention; (4) that the loss of plasma is probably characteristic of the small, rather than the large, intestine; (5) that the magnitude of the plasma loss in obstructive distention of the small bowel suggests that the loss of plasma is a basic process in the fatal effects of uncomplicated obstruction of the small intestine.

The inference is clear that the therapy of intestinal obstruction must take cognizance of this important factor in the pathologic physiology of the disease, for even when effective decompression is achieved, the effort may fail unless the plasma deficiency is corrected in time to prevent irreversible changes.

#### CONCLUSIONS

(1) Patients with distention of the small intestine, whether of functional or mechanical origin, show a considerable loss in the volume of circulating plasma.

(2) As the plasma volume falls the hematocrit rises. This increase in hematocrit is far greater than can be explained by dehydration, however severe.



(3) Dehydration and electrolyte imbalance are not responsible for the greater part of this plasma loss.

(4) Effective decompression of the small intestine restores the plasma volume toward normal.

(5) The extent of the plasma loss is generally, but not necessarily, proportional to the degree of gaseous distention as estimated roentgenologically and by physical examination.

(6) In a patient with a marked obstructive distention of the colon no loss of plasma occurred.

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## PLASMA LOSS IN SEVERE DEHYDRATION, SHOCK AND OTHER CONDITIONS AS AFFECTED BY THERAPY\*

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SHOCK may be defined as peripheral circulatory failure resulting from a discrepancy in the size of the vascular bed and the volume of intravascular fluid. In primary or neurogenic shock, vasodilatation or increase in the vascular bed is the most important initial change. In secondary or hematogenic shock, a decrease in the volume of circulating blood plays a primary rôle. Frequently, in clinical conditions the two factors of vasodilatation and loss of circulating volume work together to cause failure of the circulation. In this discussion we shall consider mainly the factors which lead to a deficiency of intravascular fluid and therapeutic methods of preventing and treating secondary or hematogenic shock.

Under *normal conditions* many factors cooperate to maintain a normal amount of fluid in the body and a normal partition of this total water in the tissue cells, the extracellular spaces and in the vascular system. The intake of water and electrolyte must keep pace with the loss of these elements from the body. There must be sufficient plasma protein to attract and hold an adequate volume of fluid in the blood stream. There is the selective permeability of the capillaries which allows water and crystalloids to pass freely but withholds most of the protein in the blood stream. There is kidney activity which removes metabolic waste products and any excess of fluid or electrolytes taken into the body. Numerous other factors might also be mentioned. A sufficiently serious abnormality in any of these factors may result in disastrous changes in the amount and partition of body fluid.

We are particularly interested, here, in *abnormal conditions* which may lead to a serious reduction in the volume of circulating blood. Among the simpler conditions which lead most obviously to such a reduction are *severe dehydration* and *extensive hemorrhage*. When replacement of water and electrolytes fails to keep pace with an excessive loss such as occurs, for example, in severe diarrhea, there is a marked reduction in body water. Since the loss is mainly one of water and salts, both the plasma proteins and cellular elements of the blood become more concentrated. With the rise in plasma protein, more and more of the reserve of extracellular water is drawn into the blood stream to replace the loss which has occurred. Thus in simple dehydration of this type it is not until the readily available extracellular reserve of water has been largely depleted that a serious reduction of blood

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volume occurs. One needs, however, only to recall the familiar picture of circulatory collapse which is seen in infants with severe watery diarrhea to realize that a point is eventually reached in simple dehydration when the reduced volume of thick, viscous blood becomes inadequate to maintain the peripheral circulation. Massive loss of whole blood through hemorrhage results in a dilution rather than a concentration of protein and cellular elements but rather promptly reduces the blood volume to an amount incompatible with sustained circulation. This condition is a simple one unless prolonged reduction in volume leads to secondary changes, to be discussed later, which lead to the inability to retain fluid restored to the blood stream.

In addition to these simpler types of loss of fluid, there are a variety of conditions which cause a reduction of the circulating blood volume through an excessive transfer of plasma elements from the blood stream into the extracellular spaces. Such an abnormal partition of body water may arise simply from a *nutritional lack* of adequate plasma protein. This is the type of disturbance that occurs in nutritional edema. Weech, Snelling and Goettsch<sup>1</sup> found that there is a progressive loss of fluid from the blood vessels as the plasma proteins are reduced, resulting first in a latent and subsequently in an evident edema. Jones and Eaton<sup>2</sup> observed that edema may occur as a complication of a variety of surgical conditions and operations and that it is exaggerated if large quantities of normal salt solution are administered. It had been noted previously, by Smith and Mendel,<sup>3</sup> that the intravenous injection of large quantities of solutions of various neutral salts results in edema if hypoproteinemia exists, whereas otherwise edema does not occur. Thus there is present in hypoproteinemia a reduction in ability to attract and hold fluid in the blood stream, and an escape and accumulation of pathologic amounts of fluid in the tissue spaces occurs.

Hypoproteinemia on a nutritional basis does not often lead to serious circulatory failure, but its correction is of importance because of the likelihood of the development of postoperative complications. It is likely that this abnormality is responsible for some instances of pulmonary edema and pneumonia. There is a retardation in the healing of incisions<sup>4</sup> and an increase in the incidence of disruption of wounds.<sup>5</sup> Mecray, Barden and Ravdin<sup>6</sup> found that the edema associated with hypoproteinemia may prevent the patency of recent intestinal anastomoses.

Frequently, a similar and more serious abnormal partition in body water occurs not because of a primary deficiency in plasma protein but because the *capillaries have been injured* to the point of letting plasma protein as well as water and crystalloids pass through the capillary endothelium into the tissue spaces. Mechanical, chemical or thermal trauma and oxygen lack are common causes of increased permeability of the capillaries. Underhill and Fisk<sup>7</sup> found that the fluid which escapes at the site of a burn is almost identical with blood serum in its composition. Beard and Blalock<sup>8</sup> found that the protein content of fluid which is lost as a result of burns, of mild trauma to an extremity and to the intestines is the same as that of the blood plasma.

# PLASMA LOSS

Clinically, one sees such injury initiated by mechanical trauma, burns to the skin, inflammatory processes, distention of the intestines with resultant interference with the circulation, *etc.* Whatever the initiating cause may be, the transfer of plasma leading to circulatory impairment is similar. Even in instances in which a prolonged decline in the blood pressure and blood volume is caused by uncomplicated hemorrhage,<sup>9</sup> a marked increase in capillary permeability occurs and plasma is lost.

TABLE I  
CHANGES DURING THE DEVELOPMENT OF CIRCULATORY FAILURE FOLLOWING A BURN  
*Dog Anesthetized with Sodium Barbitol*

Time	Plasma Volume Cc.	Concen- tration Plasma Protein Per Cent	Total Circu- lating Protein Gm.	Hemato- crit Percent- age Cells	Blood Pressure Mm.Hg.	Loss in Per Cent	
						Plasma Volume	Total Circu- lating Protein
Preliminary	523	7.03	36.6	53.4	135		
4 hrs. after burn				59.5	130		
6 hrs. after burn	347	6.78	23.5	62.0	114	32.6	35.8
13 hrs. after burn	318	6.44	20.5	66.3	76	39.0	44.0
14 hrs. after burn				68.0	45		
15 hrs. after burn					Died		

The alterations that occur in burns are illustrated by the experimental results presented in Table I. This anesthetized animal developed peripheral circulatory failure several hours after receiving an extensive burn. No supportive treatment of any kind was given. Measurements of blood and plasma volumes, hematocrit, plasma protein concentration and blood pressure were made before and at intervals after the burn was inflicted. The total circulating protein was calculated by multiplying the plasma volume by the concentration of protein. Approximately 32 per cent of the original plasma volume had been lost by the end of the first six hours. Coincident with the loss of plasma, there was a rise in the percentage of cells per unit volume of blood. The concentration of protein did not increase with that of the cellular elements as would be the case if only fluid and electrolytes had been lost. On the contrary, there was a slight decrease in the plasma protein concentration, and on calculating the total circulating protein, it was found that there had been a loss of about 35 per cent of the original amount during the first six hours. As always occurs, the burned area became swollen and edematous. Analysis of the fluid which accumulated in the subcutaneous tissues revealed a protein content approaching that of plasma. In spite of the large local loss of plasma fluid, electrolytes and protein and the associated

reduction in blood volume, the blood pressure at the end of six hours was essentially the same as during the control period. The pressure was doubtless maintained by virtue of general vasoconstriction which is known to occur in the hematogenic type of shock. With the passage of time, the changes observed during the first six hours progressed. There was an increase in the hemoconcentration and the plasma loss continued until only 61 per cent of the original volume remained while the total circulating protein was reduced to 56 per cent of the initial amount. It was not until a few hours before death that the blood pressure began to decline significantly and from this point on fatal circulatory failure progressed rather rapidly.

Scudder and his associates<sup>10, 11</sup> have investigated, very extensively, the alterations in blood potassium in various conditions. They found marked increases in plasma potassium in severe dehydration, following burns, and in other types of injury. They suggest that potassium is an ever present H-substance which may be the responsible agent in the causation of shock. On the other hand, their hypothesis is not supported by the findings of Bisgard, McIntyre and Osheroff<sup>12</sup> and Greenwood, Haist and Taylor.<sup>13</sup> It is quite possible that an elevation of plasma potassium may impair further the already handicapped circulation. Also, in the terminal stages of shock there is a more or less serious reduction of alkali reserve, largely due to the accumulation of lactic acid and other acid metabolites as the circulation and oxygenation fail.

Although details of the total picture vary somewhat with the nature of the condition which has initiated the injury, observations such as we have just described are characteristic of hematogenic shock in general and demonstrate how rapidly an increase in the permeability of capillaries leads to disastrous circulatory changes. In the presence of an injury which allows an extensive and progressive loss of circulating protein as well as fluid, there is a reduction in the colloidal osmotic pressure of the remaining blood and hence an inability to draw effectively on extravascular reserves of fluid to replenish the volume lost from the blood stream. Consequently, a much more serious reduction in blood volume results from a loss of plasma than would be caused by a considerably more extensive loss of fluid and crystalloids. In instances of localized trauma the loss of plasma is at first mainly into the injured area. Later the loss becomes more general as the previously uninjured capillary beds become more permeable as a result of oxygen lack imposed by reduced circulating volume and prolonged compensatory vasoconstriction.<sup>14</sup> Similarly, a condition which at the start involves no capillary injury but only simple dehydration may lead secondarily to vascular changes which cause a loss of plasma protein. In any case, the combined handicaps of reduced volume, increased permeability and the deleterious effects of electrolyte change bring about a rapid failure of the circulation.

*Prevention and Treatment.*—The problem in the treatment of impending hematogenic shock is to restore and maintain a more effective circulation in the presence of the abnormalities such as we have observed in the untreated



subject. Steps must be taken to overcome the discrepancy between the circulating volume and the size of the vascular bed. Attempts to increase *vasoconstriction* with such *drugs* as adrenalin, pituitrin, ephedrine, *etc.*, have met with failure as a means of preventing shock. Prolonged vasoconstriction is one of the characteristics of untreated hematogenic shock and, while it is a valuable temporary compensatory mechanism, it later becomes a factor<sup>14</sup> which contributes to further loss of plasma. It is not surprising, therefore, that the net result of these constrictor drugs is to contribute to this secondary vicious cycle of events.

Considerably more promising, according to recent reports, are the results obtained from the administration of *cortical extract*. From the experimental viewpoint, Heuer and Andrus<sup>15</sup> found that cortical extract is of value in preventing shock and of less value in treating it. Perla and his associates<sup>16</sup> stated that the parenteral administration of salt solution combined with cortical hormone is more effective than either alone in the prevention and treatment of histamine shock in rats and mice. Fine, Fuchs and Mark<sup>17</sup> found that the marked fall in plasma volume in dogs subjected to continuous distention of the small intestine is at least partly prevented by the intravenous administration of desoxycorticosterone, but there was no prolongation of the life of the animals. Somewhat encouraging results in the treatment of patients have been reported by Hartman,<sup>18</sup> Wilson, Rowley and Gray,<sup>19</sup> Wohl, Burns and Pfeiffer,<sup>20</sup> Reed,<sup>21</sup> Scudder,<sup>11</sup> and by others. At our present state of knowledge, it is impossible to understand through what mechanisms this agent exerts its favorable influence on the maintenance of a more effective intravascular volume. Possibly much of its influence may be related to its effect in restoring the distorted sodium-potassium ratio in the blood and body fluids. However useful an adjunct cortical extract may prove to be, a large part of treatment must still be replacement of the elements which have been lost from the blood stream.

The difficulty encountered in *fluid replacement therapy* varies greatly in different conditions. No uniform plan of treatment could be outlined which would be equally successful for a group of patients. Rather, the physiologic needs and the pathologic handicaps of each individual patient have to be considered and evaluated and the treatment employed regulated accordingly. If the problem is merely to restore fluid and electrolytes to an acutely dehydrated patient with a normal amount of plasma protein and with uninjured capillaries, treatment is relatively simple. On the other hand, the restitution and maintenance of an effective circulating volume of blood in a patient whose capillaries have allowed and are continuing to allow a loss of all the plasma elements including protein is far more difficult.

In any case, the patient's needs for fluid and electrolytes must be met. We will first consider the effect of the administration of solutions of crystalloids, *i.e.*, glucose and salts to patients whose blood volume has been depleted in various ways. A fundamental principle in the restitution of fluid is that if both water and salts have been lost in the process of dehydration, both water and salts must be restored. Water cannot be retained in the body without

sufficient salts to make an isotonic solution. Any attempt to restore water alone in the presence of a salt deficiency leads to physiologic disturbances, as for example, the "heat cramps" experienced by workmen who have lost salt and water through excessive sweating and then attempt to overcome dehydration by drinking water alone. Glucose solutions, valuable as they may be as a source of nutrition, are equivalent to water alone, as far as fluid and electrolyte equilibrium is concerned, and hence cannot overcome dehydration when salts have been lost. Solutions of salts *must* be employed for this purpose. Since sodium is the chief cation which is lost from the body, sodium salts are replaced. Isotonic solutions of sodium chloride are most commonly employed but a recognition of both the quality and quantity of electrolyte loss influences the solution chosen for restitution therapy. If there has been a large loss of chloride ion, as in persistent vomiting, sodium chloride is the salt indicated. If, on the other hand, there has been a marked depletion of the alkali reserve, the administration of sodium bicarbonate or sodium lactate, which will yield bicarbonate, will more promptly restore normal electrolyte equilibrium. Methods for determining the quantity and composition of the repair solutions that are needed have been described by Maddock and Coller.<sup>22</sup>

If the salt loss has been excessive and if there is an alarming distortion in the potassium-sodium relationship, the more rapid administration of sodium salts in hypertonic solutions is indicated. As a general thing, however, isotonic solutions are less disturbing to the patient.

The *route of administration* of such solutions is another problem which should receive individual consideration according to the needs and handicaps of the patient. Will fluid be retained when given by mouth; will fluid be absorbed from the gastro-intestinal tract if given orally or by proctoclysis; will fluid be absorbed when given subcutaneously; and what disposition will be made of fluid that is given intravenously? Any of these routes is satisfactory for the simple restoration of water and electrolytes to overcome dehydration. Frequently vomiting or diarrhea or infection or an operation makes the gastro-intestinal route impractical, but good results may be obtained when fluid and electrolytes are supplied in suitable amounts either by the subcutaneous or intravenous routes.

In the patient with a primary nutritional lack of plasma protein or in one who has lost plasma protein as well as fluid through injured capillaries, the problem is more difficult. Such patients absorb fluids poorly from the gastro-intestinal tract. Fluid given subcutaneously also tends to remain unabsorbed in the tissues where it is placed. It is easy to see why this is true. Most of the difficulty in patients of this type arises before treatment is started from a transfer of plasma elements from the blood to the tissues due to an inability to attract and hold water in the blood stream. The same handicap which made it impossible for the patient to maintain a normal partition of body water before treatment makes it impossible for him to absorb and maintain in the blood stream fluid which is administered into the tissue spaces. This leaves only the intravenous route as an effective means of introducing fluid.

There is no doubt but that the intravascular volume can be temporarily increased by the direct introduction of salt solutions into the vascular system. The prompt temporary response of most patients with depleted blood volume to such treatment is well known. It is equally well known that this favorable response is often disappointingly transient and the blood stream again becomes dehydrated and the circulatory impairment progresses in spite of the continued introduction of fluid.

A study<sup>23, 24, 25</sup> of what occurs when aqueous solutions are given intravenously to experimental animals or patients with *increased capillary permeability* explains the reason for the failure of this form of therapy. The introduction of aqueous solutions dilutes the plasma colloids in the blood stream. If they are already low, further dilution brings them to a concentration which makes it impossible to hold the administered fluid in the blood stream. Tissue edema develops while the blood stream remains dehydrated. If there is extensive capillary damage so that protein escapes with fluid, the continuous administration of fluid by vein washes out more protein and as a result may actually reduce rather than increase the volume of circulating blood.

The best guide as to the disposal being made of fluid administered by vein is afforded by frequent measurements of hematocrit or hemoglobin and of plasma protein. If fluid is being retained in the blood stream, both hemoglobin and plasma protein should decrease in concentration together. When, as so often happens, the paradoxical observation is made that the concentration of protein is decreasing while that of hemoglobin is increasing as fluids are given intravenously, it can only mean that plasma is being lost from the blood stream and that the treatment is accomplishing nothing toward restoring a more effective circulating volume. Under these circumstances, colloid as well as aqueous solutions must be administered before fluid can be retained in the blood stream. It is too well recognized to require further emphasis here that transfusions of blood or plasma should be given early in the supportive treatment of impending hematogenic shock when there has been protein loss. A point which may need further emphasis, however, is the really enormous amount of colloid which may be required and which will ultimately bring about successful results in patients with extensive capillary injury. One can calculate, more or less accurately, the amount of fluid and electrolyte a person needs to replace what has been lost and to keep pace with his continuous needs. There is no such definite approach to the amount of colloid required if its loss through damaged capillaries is continuous. The rate of plasma loss can be cut down somewhat by conservatism in the amount of aqueous fluid given by vein. In this connection, it may be advantageous at times to give aqueous solutions that are hypertonic rather than isotonic because the higher salt content temporarily attracts and holds more fluid in the blood stream.

In Table II are collected observations made upon two anesthetized dogs receiving continuous mild intestinal trauma. One was given a continuous

slow intravenous injection of 0.9 per cent sodium chloride solution throughout the experiment. The other received a continuous slow transfusion of blood serum. In spite of the continued administration of saline there was a progressive decrease in plasma volume and an increase in the concentration of cellular elements. During the same period there was a gradual decrease in the concentration of plasma protein and a loss of well over half the total circulating protein during a period of seven hours. In the dog receiving serum, there was a moderate increase in plasma volume and total circulating

TABLE II

COMPARISON OF EFFECT OF CONTINUOUS INTRAVENOUS INJECTION OF NORMAL SALINE AND OF BLOOD SERUM IN DOGS RECEIVING CONTINUOUS INTESTINAL TRAUMA

Fluid Employed	Time from Start	Amount of Fluid Administered Cc.	Concentration Plasma Protein Per Cent	Plasma Volume Cc.	Total Circulating Protein Gm.	Hematocrit Per Cent Cells
0.9 per cent saline	Control	0	6.2	942	58.6	52.4
	1° 30'	297	5.7	835	48.3	56.3
	3° 30'	693	5.1	865	44.1	54.5
	5° 30'	1,089	4.3	650	28.1	61.7
	7°	1,388	3.3	672	22.2	60.7
Blood serum	Control	0	5.0	474	24.0	42.2
	1° 30'	123	5.1	578	29.7	38.0
	3° 30'	280	5.4	572	31.1	37.8
	5° 30'	444	5.9	546	32.7	40.0

protein with little change in hematocrit. Assuming that the serum administered contained 5-6 per cent protein, it is evident that an amount of protein equivalent to the total plasma protein present before the initiation of capillary injury was given during five and one-half hours. The continued loss from the blood stream is shown by the fact that this large replacement caused only a moderate increase in the total circulating protein.

We know of no specific means of directly influencing the increased permeability of injured capillaries unless cortical extract proves to be an agent which can accomplish this. Our approach has to be rather an attempt to give colloid fast enough to increase the level in the blood to the point of retaining an effective circulating volume in spite of the losses that may occur. To do this often requires transfusions far in excess of what would ordinarily be considered adequate. This is illustrated by a recent experience in the Vanderbilt Hospital in the treatment of an adult with burns of almost one-half of the body surface. During the first 19 days that the patient was in the hospital, the total quantity of fluids that were given intravenously consisted of 5,000 cc. of blood plasma, 2,650 cc. of whole blood, and 8,700 cc. of salt or glucose solutions. The greatest quantity of salt or glucose solution given intravenously in any one 24 hour period was 1,500 cc. Fluids were administered by other routes in larger amounts. Even though large quantities of colloidal solutions were given, and the intravenous injections of solutions of crystalloids were



somewhat restricted, the total serum proteins on several occasions fell to less than 4 Gm. per 100 cc. This illustrates the really tremendous amounts of blood and plasma which are required to maintain a fairly satisfactory level of plasma protein and an effective volume of circulating blood. It is believed that the patient's recovery was due to the administration of large quantities of colloidal solutions. The local therapy of the burn consisted only of the application of compresses of Dakin's solution. The experience of Gatch<sup>26</sup> and of Trusler, Egbert and Williams<sup>27</sup> is similar to that which we have related.

Transfusion of *blood plasma* is probably the method of choice for restoration of plasma volume. The use of plasma rather than whole blood avoids further burdening of the circulation with cellular elements which are already present in high concentration. Volume for volume, plasma transfusions introduce protein approximately twice as fast as when whole blood is given. There is less danger of reactions from plasma than from any of the more artificial preparations which have been suggested. The disadvantages of plasma are the additional technical difficulties and time required for preparing plasma for transfusions and the larger amounts of blood which must be furnished by donors. Even in instances in which the primary disturbance is the loss of whole blood, Levinson, Neuwelt and Necheles<sup>28</sup> and others have found that the introduction of blood plasma or serum exerts markedly beneficial effects. The value and convenience of having available a "Plasma Bank" can hardly be overestimated in the treatment of patients with capillary injury. Here, a delay of a few hours may preclude the possibility of a favorable response. Without a "Bank" it is impossible to procure plasma without considerable delay. Lacking plasma, transfusions of whole blood should be administered promptly and repeatedly.

The consensus of opinion appears to have been that there is little choice between blood serum and blood plasma and that there is little danger of reactions with either of these. In recent publications, Strumia, Wagner and Monaghan<sup>29, 30</sup> state that blood serum is much more apt to cause unfavorable reactions than is plasma, and that the difference is brought about by the process of fibrin precipitation. This work has not as yet been confirmed.

Many attractions are offered by desiccated or *lyophilized blood serum*. The dried powder can be kept indefinitely. It can be dissolved in a smaller volume of water than that of the original plasma and so a solution richer in protein than fresh plasma can be introduced. The chief disadvantages are the cost and difficulty of preparing the dried serum and the frequency of reactions following the injection of the redissolved powder. Ravdin<sup>31</sup> is of the opinion that the frequency of reactions is such that lyophilized serum should not be used. Strumia, Wagner and Monaghan<sup>29, 30</sup> state that the reactions which have been observed following the intravenous administration of lyophilized serum are due not to a change induced by the process of desiccation but to the use of serum. It is further stated that lyophilized or cryochem plasma causes no reactions.

*Acacia solutions* have been employed to some extent as a means of introducing colloid. Acacia is not a protein but it has the property, similar to



that of plasma protein, of attracting and holding water in the blood stream. As an emergency measure, when whole blood or plasma cannot be procured for transfusion, much can be accomplished in restoring the blood volume by intravenous injections of acacia. The frequency of reactions to such injections and the prolonged storage of acacia in the liver and other tissues make its use inadvisable except in emergencies. Experimental work indicates that the use of *ascitic fluid* may, at some time, become a practical means of supplementing the plasma volume. The protein content of ascitic fluid is somewhat less than half of that of blood plasma.

## CONCLUSIONS

Failure of the peripheral circulation due to an inadequate volume of circulating blood may result from severe dehydration, extensive hemorrhage, and from conditions which allow a transfer of plasma elements from the blood stream into the tissue spaces. The aim of supportive treatment in impending shock of this type is to restore and maintain a more adequate volume of intravascular fluid. The character and amount of fluid employed for replacement therapy as well as the route of administration must be adapted to the requirements and handicaps of the individual patient. In the absence of capillary injury, the restitution of whole blood after hemorrhage or the replacement of fluid and electrolytes in dehydration is a relatively simple problem. In patients in a poor state of nutrition or in whom there is either localized or general injury to capillaries, it is much more difficult to maintain the proper distribution of administered fluids. The intravenous administration of solutions of crystalloids to such patients often leads to the production of massive edema while the blood stream remains dehydrated or even becomes further decreased in volume. Under these conditions the administration of liberal amounts of plasma colloid is an indispensable factor in the restoration of fluid and electrolyte equilibrium.

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## PHYSIOLOGIC FACTORS REGULATING THE LEVEL OF THE PLASMA PROTHROMBIN \*

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THE PROTHROMBIN CONCENTRATION of the blood became important in the management of surgical patients as the result of the demonstration by Quick, Stanley-Brown and Bancroft<sup>1</sup> that hypoprothrombinemia was at times associated with obstructive jaundice. However, it was not until Warner Smith and Brinkhous<sup>2</sup> demonstrated that the prothrombin level in these patients could be restored to normal by the administration of vitamin K and bile salts, that a widespread interest developed in the prothrombin level of the jaundiced patient.

The hypothesis upon which this treatment was based was that vitamin K was necessary for prothrombin formation and that bile salts were necessary for its absorption from the bowel. When the common duct is obstructed, so that bile is prevented from reaching the intestine, vitamin K is not absorbed into the portal circulation, and prothrombin formation stops as soon as the stores of vitamin K are exhausted. Quick,<sup>3</sup> who first proposed this hypothesis, was also the first to encounter a patient that disproved it.<sup>4</sup> The patient in question had a prothrombin level which at one time was as low as 2.5 per cent and failed to respond to a vitamin K substrate, so that it was necessary to resort to transfusions to check hemorrhage.

Various authors have reported varying degrees of success in treating hypoprothrombinemia with vitamin K substrates. During 1938 and the first half of 1939, Cerophyl was employed in treating the cases of hypoprothrombinemia studied in the Harrison Department of Surgical Research at the University of Pennsylvania. The prothrombin time returned to normal in 69 per cent of the cases treated and showed an improvement in an additional 13 per cent. Three cases, or 18 per cent, however, failed to show any improvement. Following the isolation<sup>5</sup> and synthesis of vitamin K<sub>1</sub> by Doisy and his associates, a number of synthetic substances with vitamin K activity became available for clinical use. One of these, 2-methyl-1, 4-naphthoquinone proved to be even more active than naturally occurring K<sub>1</sub> extracted from alfalfa. It was hoped that this substance, powerful as it was, would cause a favorable rise in the prothrombin level of those patients that had failed to respond satisfactorily to vitamin K substrates. The results obtained are shown in Table I. In 73 per cent the prothrombin level returned to normal; in an additional 9 per cent it improved, but in 18 per cent there was no improvement. It is probable, therefore, that the solution of this problem does not lie in the direction of the administration of more active preparations

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having a K activity. Experience with four other synthetic preparations, one of which was given intravenously, has so far confirmed this impression. It should be stated, however, that the more potent preparations achieve a much prompter response in those patients that do respond favorably than was the case when vitamin K substrates were used.

TABLE I

A COMPARISON OF THERAPEUTIC RESULTS IN THE TREATMENT OF HYPOPROTHROMBINEMIA WITH CEROPHYL (VITAMIN K SUBSTRATE) AND 2-METHYL-1, 4-NAPHTHOQUINONE

	Patients Treated	Prothrombin Returned to Normal		Partial Improvement		No Improvement	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
Cerophyl.....	16	11	69	2	13	3	18
2-methyl-1, 4-naphthoquinone.....	22	16	73	2	9	4	18

In general, it has been found that hypoprothrombinemia in patients with common duct obstruction due to cholelithiasis responds well, but that hypoprothrombinemia in patients with cirrhosis as a rule responds very poorly. Clinical evidence, therefore, points to hepatic cellular injury as the major cause of the failure to obtain a satisfactory response following adequate therapy. Vitamin K deprivation may explain the clinical hypoprothrombinemia seen in hemorrhagic disease of the newborn.

Some of the experimental evidence bearing upon this mechanism has been confusing as any factor capable of producing liver damage may also be capable of inhibiting bile salt formation. The principal experimental methods of inducing a fall in the plasma prothrombin level are summarized in Table II.

TABLE II

EXPERIMENTAL METHODS OF PRODUCING HYPOPROTHROMBINEMIA

Method	Animal	Approximate Time Required
Vitamin K-free diet.....	Chick	1 to 3 wks.
	Rat	
Biliary fistula.....	Dog	2 to 4 mos.
	Rat	3 to 4 wks.
Ligation of common bile duct.....	Rat	Not stated
Chloroform anesthesia.....	Dog	<24 hrs.
Carbon tetrachloride.....	Dog	<24 hrs.
Phosphorus.....	Dog	Not stated
Spoiled sweet clover hay.....	Rabbits	2 to 3 days
	Cattle	
Partial hepatectomy.....	Rat	<24 hrs.
Total hepatectomy.....	Dog	Progressive decline evident within 1 to 4 hrs.
Liver trauma.....	Dog	2 hrs.

The bile fistula methods of producing hypoprothrombinemia are relatively slow—two dogs in our laboratory failed to show a significant fall in over 15 weeks. Contrasted with this is the rapid drop in the same species induced by the administration of chloroform or carbon tetrachloride. By cannulating the common duct it was possible to show that the fall in the prothrombin concentration which followed chloroform anesthesia started while bile salts were still present in the hepatic bile in good concentration, but was influenced in degree by sidetracking the bile to the exterior.<sup>6</sup> It was also noted that animals which had had choledochostomy performed previously showed a greater fall in prothrombin concentration following chloroform anesthesia of given duration than did unoperated animals, and that a second anesthetization with chloroform, even after the prothrombin level had returned to normal, was followed by a much greater drop in the prothrombin concentration than was the first.

Liver damage due to chemical agents was associated with such prompt disappearance of prothrombin from the circulation that it seemed likely that certain agents actually exerted a deleterious action on prothrombin itself. In order to evaluate more accurately the rôle of the liver, total hepatectomy was carried out by Warren and Rhoads<sup>7</sup> on eight dogs. In some animals this was performed by the three-stage method of Mann and in others it was accomplished by one-stage methods. The animals prepared by the three-stage method survived longest. Prior to the final stage the prothrombin had already been depleted to a considerable extent, probably as the result of the previous changes in the circulation of the liver. The subsequent fall, however, was quite rapid. Neither hemorrhage, celiotomy for other purposes, nor three-hour periods of ether anesthesia were effective in producing this marked drop. As the prothrombin level fell following the one-stage operation as well as the multi-stage procedure, it seemed justifiable to conclude that the fall was due to a cessation in the formation of prothrombin and not to the accompanying cessation of the bile salt supply to the intestine. Andrus, Lord and Moore,<sup>8</sup> independently, arrived at similar conclusions.

In view of the relatively gradual decline in the prothrombin level observed in bank blood, the rapid disappearance of prothrombin from the hepatectomized animal obviously requires some explanation. This is partly to be found in the observation that blood specimens stored at room temperature show more rapid declines in prothrombin concentration than they do in the refrigerator at 4° C., and similar specimens stored in an incubator at 37° C. show a profound drop in 24 hours.

Andrus, Lord and Kauer<sup>9</sup> have called attention to an additional factor in this decline. They demonstrated that blood coming from the lungs regularly contains prothrombin in lower concentration than does blood in the pulmonary artery, indicating that some destruction of prothrombin regularly occurs in the pulmonary circulation.

The available evidence, therefore, points to a continuous and relatively rapid disappearance of prothrombin from the circulation and a concurrent



formation of prothrombin which occurs mainly if not exclusively in the liver. Acute liver injury is, therefore, we believe, sufficient to produce a sudden and serious drop in the prothrombin level in contrast to the gradual declines characteristic of vitamin K deficiency.

The question of whether an excess of vitamin K can, at least in part, compensate for faulty liver function is an important one. In favorable cases a single milligram of 2-methyl-1, 4-naphthoquinone may suffice to restore a moderately reduced prothrombin concentration to normal. In other cases in our experience as much as 42 mg. in 24 hours has failed. It has been the impression of several workers that increased doses of the vitamin have overcome prothrombin deficiencies that were resistant to the usual doses. If a mass action effect takes place one would expect that it would affect the normal liver as well as the damaged liver and that the administration of 2-methyl-1, 4-naphthoquinone to normal individuals would lead to an increase in prothrombin concentration above the average normal. With the aid of Dr. Robert Norris, an attempt was made to ascertain whether this could be accomplished in a group of miscellaneous surgical patients at the Pennsylvania Hospital. The dose was 6 mg. per day. The results were essentially negative, though a slight shortening in the prothrombin time was observed. This does not, of course, prove that at subnormal levels an excess of vitamin K may not be advantageous, but the mass action hypothesis does lack this bit of supporting evidence. Much larger doses might, of course, have a different effect.

In three cases of hypoprothrombinemia, in which an increased dosage of vitamin K seemed particularly useful, blood transfusions were also given. The effect was too great to be accounted for by the prothrombin in the transfused blood and was accordingly credited, in part, to the added vitamin K. Tocantins<sup>10</sup> has reported a similar experience from the Jefferson Hospital and postulated that 2-methyl-1, 4-naphthoquinone and blood transfusion might have a synergistic action. One can speculate that the added protein in the blood aids in improving hepatic function, or that it provides needed building material for prothrombin formation, or that prothrombin is composed of two or more substances, only one of which may require vitamin K for its formation. This fraction might ordinarily be the critical factor in governing prothrombin activity but in the vitamin K-fast patient another fraction contained in normal blood might become the critical factor.

The observations of a synergistic effect of transfusion and vitamin K, or its substitutes, on the prothrombin level of the blood have not been sufficiently numerous to exclude coincidence as the explanation, but they do point to one approach to the problem of the patient with hypoprothrombinemia who is resistant to vitamin K therapy.

A more fundamental approach to this problem, however, appears to lie along the lines of improving the condition of the liver prior to operation. On the basis of animal experiments, which have been reported by Doctor Ravdin,<sup>11</sup> a diet has been made up for the preparation of patients with

suspected moderate or severe liver damage on his service at the Hospital of the University of Pennsylvania. The diet consists of 75 per cent carbohydrate, 20 to 25 per cent of protein and not more than 5 per cent of fat. The total caloric intake is of great importance and should exceed 2,500 calories per day. The diet is continued for seven to 14 days before operation whenever possible. Strenuous efforts must often be made to induce the patients to eat adequately, but with added vitamins and added bile which is lyophilized and given in capsules as suggested by Dr. Charles Johnston, it has usually been possible to succeed and to have the patient gain weight preoperatively. Sufficient time has not elapsed since this regimen was started to evaluate adequately its effect on the response of hypoprothrombinemic individuals to vitamin K. During the six months' experience we have had, however, it has been possible to raise the prothrombin concentration to an adequate level for operation in every case.

Figures 1, 2 and 3 illustrate how badly some of these vitamin K-fast patients need a regimen which will improve the condition of their livers. These are photomicrographs of livers obtained at autopsy from patients who had a fall in prothrombin in spite of active vitamin K therapy. None of these patients was operated upon. Whether diet could have helped them may be doubtful, but it seems almost certain that the occasional patient whose prothrombin level will remain at dangerously low levels after adequate dietary preparation and adequate vitamin K therapy will have a hopeless prognosis for other reasons also.

The experimental data, so far available, indicate that hypoprothrombinemia as it occurs in most patients, can be accounted for by an interference with the formation of prothrombin without postulating an accelerated destruction of prothrombin. Interference with prothrombin formation may be due to absence of vitamin K from the alimentary tract; faulty absorption of the vitamin from the intestine, which is most commonly due to an inadequate supply of bile salts; or impaired production of prothrombin due to hepatic damage.

From the clinical standpoint, a large majority of surgical patients with prothrombin deficiencies will respond satisfactorily to the administration of vitamin K and bile salts. Some of those with impaired liver function will respond poorly or not at all. There are three methods of treating this group of patients. The first is to increase the dose of vitamin K. This has not produced a satisfactory response in many of those patients who were not responsive to moderate doses. The second is to give transfusions of blood which should preferably be freshly drawn. Whether or not this has a synergistic action with vitamin K, it is a valuable method for obtaining a temporary rise in prothrombin concentration. The third method, which may be tried if time permits, is to endeavor to improve hepatic functional activity by dietary means in addition to the continued administration of vitamin K, for with improvement in the cellular activity the likelihood of a more favorable response to vitamin K therapy can hardly be doubted.

FIG. 1.—Photomicrograph of section of liver of six-months-old child with atresia of the common bile duct who died 36 hours after a fall in plasma prothrombin concentration occurred in spite of the administration of 2-methyl-1, 4-naphthoquinone and bile salts. The hepatic parenchyma is largely replaced by fibrous tissue.

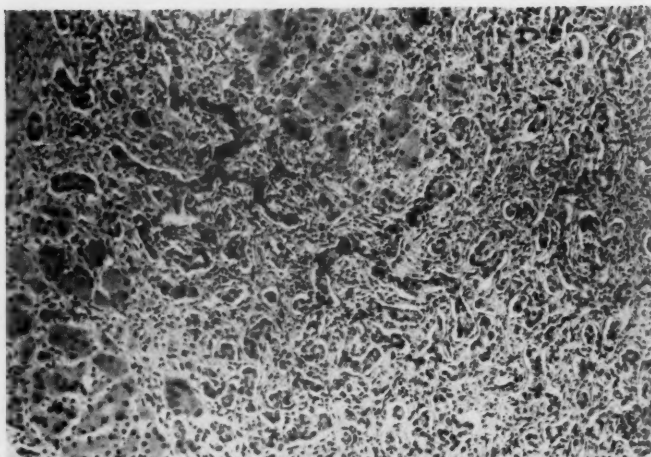


FIG. 2.—Photomicrograph of section of liver of patient who died of carcinoma of the head of the pancreas. This patient's plasma prothrombin level was well controlled for several weeks, but in spite of continued vitamin K therapy, the level fell during the two weeks before death.

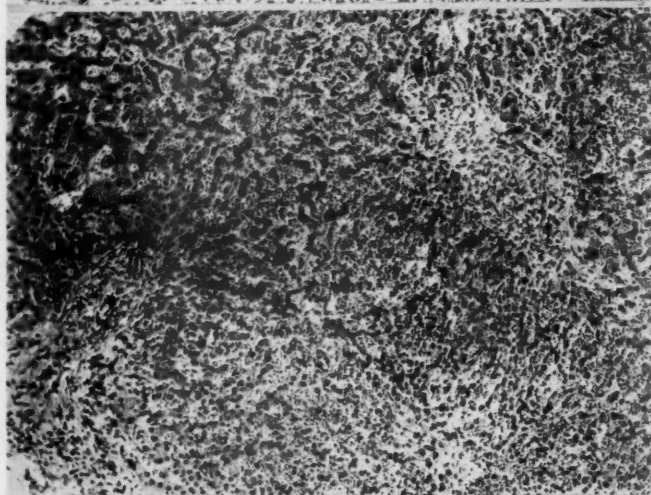
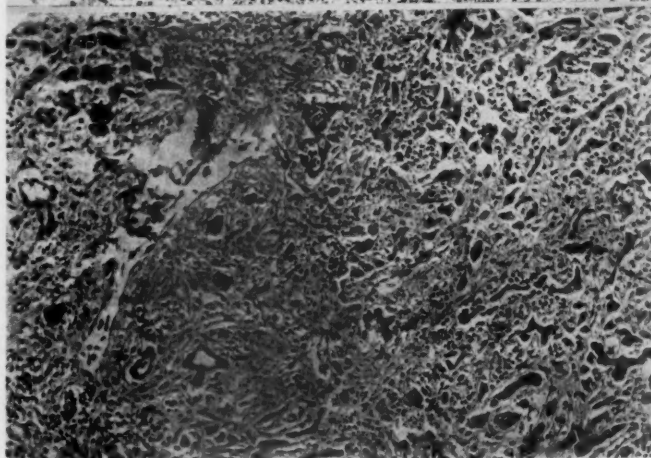


FIG. 3.—Photomicrograph of section of liver of patient who died of carcinoma of the head of the pancreas. The prothrombin level fell shortly before death in spite of the oral and intravenous administration of 2-methyl-1, 4-naphthoquinone.



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DISCUSSION.—DR. WILLIAM DEW. ANDRUS (New York City): It is a particular pleasure to hear Doctor Rhoads' paper and to follow the lines of thought in his presentation, as our own experience and line of thought have been similar. As he stated, we independently confirmed his finding that hepatectomy is followed by a very rapid fall in the plasma prothrombin, and we also showed that the administration of 10,000 units of vitamin K in the form of Klotogen and bile salts injected into the intestine at the time of operation failed to alter this fall in any way.

It is also extremely interesting that in the 49 cases which we have followed in our own series, in which we have used 2-methyl-1, 4-naphthoquinone, the percentage which failed to respond is exactly the same as in his.

Doctor Rhoads has brought up several very interesting points with regard to the physiology of the formation of prothrombin and the effect of liver damage upon it. The fact that the prothrombin cannot be elevated above 100 per cent of normal even by massive doses of the vitamin or of 2-methyl-1, 4-naphthoquinone is extremely interesting and can be very amply confirmed. We have given as much as 100 times—well, more than that—we have given to both normal and prothrombin deficient dogs of 10 Kg. weight, doses of 50 mg. of 2-methyl-1, 4-naphthoquinone, 1 mg. being sufficient to produce adequate response in an adult, without in any instance being able to produce a rise of the prothrombin above the normal. What that is due to we do not know. A possible theoretic explanation is that if the naphthoquinone be the fundamental building stone of prothrombin, the liver has an upper limit above which it cannot manufacture prothrombin no matter how much of the raw material is available.

We had one very striking instance—a clinical case which Doctor Rhoads may have remembered I presented in discussing his paper last June—of a 50-year-old woman who had common duct obstruction and a very severe jaundice and inflammatory reaction about the base of the gallbladder. She responded strikingly to the administration of bile salts and vitamin K, her prothrombin returning to 100 per cent. Then, despite the continued administration of the same regimen, it suddenly fell down to 30 per cent and remained there until she died a few days later. At postmortem, she was found to have a thrombosis of the hepatic artery and portal vein with massive necrosis of the liver—if you will, a functional hepatectomy.

We have used intramuscular injections of 2-methyl-1, 4-naphthoquinone in 49 cases with diminished prothrombin level, with satisfactory response in 41. In three of these 49 patients, there was clinical evidence of liver dam-

age as indicated by liver function tests, but its exact nature is not yet known. In the five others, who failed to respond to 2-methyl-1, 4-naphthoquinone, and in two additional cases not included in the above series who were treated with Cerophil or Klotogen but whose prothrombin did not rise despite continued administration of the vitamin, the presence of marked liver damage was definitely proved—at operation in two cases and at postmortem examination in five cases.

These seven patients presented a wide variety of pathologic pictures, including Laënnec's cirrhosis, cholangitis, periportal hepatitis, multiple liver abscess complicating pylephlebitis, gas bacillus infection, cirrhosis with central necrosis, and massive infarction of the liver secondary to the thrombosis of the hepatic artery and portal vein. The lesions were so diverse in nature and so widespread in extent as to yield little information regarding any specific type of liver injury responsible for the decreased prothrombin production.

In conclusion I should like to emphasize another point that Doctor Rhoads has made. We have here in its reaction in formation of prothrombin, which is interfered with in the presence of liver damage, a further reason for fortifying the liver by means of a high carbohydrate and high protein diet, if time permits before operation. In any event, doses of glucose should be given before operation, in order to stave off, liver injury which may play a very vital rôle in the prothrombin metabolism as it does in other respects.



## HYPOPROTEINEMIA AND ITS RELATION TO SURGICAL PROBLEMS \*

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DURING the past two decades innumerable papers have been written on the fluid and electrolyte loss in persistent vomiting, in diarrhea, following extensive superficial burns, and in many other conditions, but until very recently, with the exception of the papers dealing with shock following trauma, very little has appeared in clinical literature on the important part that an adequate concentration of the plasma protein plays in keeping fluid in blood vessels. No consideration of fluid and electrolyte loss and their restitution is sufficient unless the plasma protein is simultaneously considered. The present symposium on a surgical program is evidence of the recognition by surgeons of the importance of plasma volume in a wide variety of conditions. The clinical and experimental conditions to be briefly considered in this paper may seem to be unrelated. Indeed, in some cases the studies were initiated independently. Nevertheless, a common factor would seem to appear as an important casual agent in each. This factor is the protein of the body available to meet the body's demands under the prevailing conditions.

*General Considerations.*—Many of the patients coming to the surgeon for operation have, as a result of restriction of diet resulting from a variety of causes, from visceral injury, or from excessive plasma loss, a reduction not only in the concentration of plasma protein but also in the total available plasma protein. In fact, a reduction in the total plasma protein usually occurs before a reduction in the concentration takes place. Even though the concentration of the plasma protein is normal when the patient is first seen, it frequently falls sharply when fluids are administered in attempting to overcome an existing dehydration. Observations we have made strongly support the concept that there is no such thing as a critical level of the plasma protein at which edema becomes manifest. As soon as the plasma protein falls below the normal concentration, fluid begins to leave the vessels resulting first in a latent, and, finally, when the accumulation of fluid in the tissues is great enough, in an evident edema.

Weech and Ling<sup>1</sup> have shown that the administration of large amounts of neutral sodium salts, such as sodium chloride, will intensify the edema normally occurring at the same level as the plasma protein. Thus, frank edema may be present in patients receiving excessive amounts of salt solution, whose plasma protein concentration is well above the so-called critical level of edema of 5.2 Gm. per cent. In the presence of hypoproteinemia, attempts to restore a normal fluid and electrolyte balance, without at the same time

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increasing the colloid osmotic pressure by adding to the plasma protein, too frequently result only in adding to the extravascular fluid reservoirs.

Although the final pictures may be similar, the primary factors involved in hypoproteinemia in many conditions are, of course, quite dissimilar. In extensive superficial burns the hypoproteinemia is the result of the excessive loss of plasma protein into the tissues. The hypoproteinemia associated with hepatic disease is no doubt due to a defect in protein synthesis, while the hypoproteinemia encountered in gastric and duodenal ulcer and cancer results frequently from protein restriction in the diet. Thus, while a "loss or lack"<sup>2</sup> of protein accounts for many instances of hypoproteinemia, alterations from the normal of protein synthesis are also a factor in some conditions.

The evidence now available shows that in starvation or on diets low in protein the protein content of certain viscera, especially the liver,<sup>3</sup> is markedly reduced. Whatever the cause of the reduction in total plasma protein, it is unlikely that this reduction is not also associated with at least a partial depletion of the important stores of rapidly mobilizable protein of the body. In protein undernutrition the tissue stores of protein may suffer before hypoproteinemia is excessive. The stores of protein mobilized under these conditions have been designated by Whipple<sup>4</sup> as "labile protein."

When adequate protein feeding is begun the depleted stores of visceral protein must be at least partly replenished during the period of plasma protein regeneration. Tissue and plasma protein depletion and regeneration must, therefore, under many conditions go on simultaneously, the one complementing the other. In dogs which we had kept on an extremely low protein intake and further reduced their protein reserves by plasmaphereses, we obtained evidence which suggests that intravenously injected plasma protein was used for replenishment of protein stores depleted during the period of protein starvation.

During undernutrition, tissue protein is protected in part as long as carbohydrate and fat are available for energy requirements. The sparing action of carbohydrate on protein is too well known to require further discussion.

The many references in surgical literature to tissue regeneration upon a diet composed entirely of carbohydrate demonstrate a fundamental lack of knowledge of cell regeneration, for tissue growth requires protein components, the amino-acids, or larger aggregates, for building material.

*Hypoproteinemia and Its Effect on Gastro-intestinal Motility.*—As Starling<sup>5</sup> pointed out many years ago, the osmotic pressure of the plasma crystalloids, although large when compared with that of the plasma protein, is of minor importance in keeping fluids in blood vessels, for the crystalloids pass freely in either direction through the walls of blood vessels. As the plasma protein concentration falls from the normal 7.0 to 7.5 Gm. per cent the osmotic pressure exerted by the plasma is reduced and fluid begins to leave the vessels, causing at first a latent and finally, when the increase of extravascular fluid is great enough, an evident edema. Jones and Eaton<sup>6</sup> and Jones,

Eaton and White<sup>7</sup> first called attention to certain complications which may occur during hypoproteinemia and its accompanying edema.

The papers of Jones, Eaton and White,<sup>6, 7</sup> and those which we have published,<sup>8, 9, 10</sup> focused attention on the importance of nutritional edema in gastro-intestinal surgery. The increase in subcutaneous fluid in hypoproteinemia is but one manifestation of a widespread increase in tissue fluid and the gastro-intestinal tract is not exempted from this process. Mecray, Barden, Frazier and I<sup>8, 9, 10</sup> have shown that even when the gastro-intestinal tract of the dog is intact, a reduction in the plasma protein concentration will result in a marked increase in the normal gastric emptying time and a further delay in cecum appearance time. We have in a number of instances after operation upon our own patients, and in patients operated upon by other surgeons, found that the retardation of gastric emptying time may be so prolonged as to simulate a technical defect in the anastomosis. We have, in fact, come to the conclusion that so-called "vicious circle" more often results from a disturbance in the normal movement of fluids than from technical defects of the new anastomosis.

In dogs, which many months previously had had a pylorotomy with restoration of gastro-intestinal continuity by the Pólya technic, a reduction in the plasma protein by diet and plasmaphereses results in a marked increase in gastric emptying time. The roentgenographic appearance in these dogs, following the barium meal, is similar to that observed in many of the patients who supposedly have retention from a defect in the anastomosis after a similar operation.

The prolonged interference with a normal diet which many of the patients coming to operation for gastric and duodenal ulcer and gastric cancer have had, results, frequently, in varying degrees of undernutrition. The total caloric intake and the composition of the diet have very often been inadequate. The protein starvation may be the result of a self-imposed diet, but we have been impressed with the frequency with which hypoproteinemia has been observed while patients were under supposedly competent medical care. In man, the problem has been further complicated by the fact that there are frequently associated deficiencies in certain of the important accessory food-stuffs which affect gastro-intestinal motility and pattern.

Hypoproteinemia intensifies the edema of trauma naturally occurring at the site of gastro-intestinal suture. Under normal conditions of fluid exchange the edema of trauma begins to disappear 48 to 72 hours after operation, but in the presence of hypoproteinemia it continues to increase during this period, resulting in a mechanical impediment to the forward progress of the gastric contents.

Furthermore, when gastric contents pass into the small bowel the progress is further restricted by a coincidental, though less marked, decrease in small intestinal motility.

Surely, the convalescence of these patients will be smoother and the incidence of untoward complications will be reduced if nutritional deficits

are, if possible, corrected prior to operation, or as soon as possible after operation.

I shall not discuss the many methods which may be employed both before and after operation to correct protein deficiency. At present we have found that the most rapid means of correcting it is by repeated plasma transfusions. These are well tolerated and rarely associated with the postinjection reactions so frequently observed after employing serum. We believe that it is better to administer small amounts of plasma repeatedly, over a long period, than to inject large amounts during a very short period. When more time is available and after operation upon patients whose "labile stores" of protein are thought to be very low, the orojunal method, which Stengel and I<sup>11, 12</sup> have described, is useful and practical. Although we have used varying amounts and combinations of amino-acids, intravenously in these patients, we have as yet no significant data that their administration in this manner will lead to the rapid synthesis of plasma protein. Even though we have, in a few instances, in the dog and in man obtained a positive nitrogen balance for a brief period, we have never observed a significant rise in the plasma protein concentration or the total plasma protein unless these substances were placed directly into the gastro-intestinal tract. Is the older viewpoint, that the gastro-intestinal mucosa conditions the amino-acids for protein-building stores, perhaps the correct one?

*Wound Healing.*—In a study of wound healing which Smelo<sup>13</sup> made in my department, in 1935, he concluded that "factors other than the local dressing appear to play the dominant rôle in determining the rate of wound healing." Anderson,<sup>14</sup> continuing these studies, stated that "the healing of granulating wounds under normal conditions, as determined by precise volume measurements, occurs according to a regular geometric curve which may be expressed as a function of area and time, by the mathematic equation presented by Carrel<sup>15</sup> and DuNoüy<sup>16</sup> for the normal cicatrization of clean surface wounds."

That disruption is still encountered in wounds free from infection, in which hemostasis was excellent, in which trauma to tissues and tension was minimal, and unusual strain obviated, strongly supports the concept that other factors of a general character play an important part in the failure of certain wounds to heal. That purely local factors may intensify the factors of a biologic character will not be doubted by anyone who has carried on investigations in this field.

We have shown that dogs which have been made hypoproteinemic by prolonged feeding of a low protein diet and plasmapheresis have a marked delay in fibroblastic proliferation and thus wound healing is retarded. The hypoproteinemia in our animals was but one manifestation of the protein starvation of the dogs. Although at first we were inclined to attribute the delay in fibroblastic proliferation to the presence of edema, we are now convinced that the mechanism is associated with a profound disturbance in protein metabolism, the hypoproteinemia being only an easily measurable indi-



cator of the extent to which the so-called "labile stores" of protein have already suffered.

It is well known that cellular repair and regeneration require protein, for in the absence of an adequate amount of certain essential amino-acids growth cannot take place. Admont Clark<sup>17</sup> has shown that on a diet high in protein there was no quiescent period in the repair of wounds, and Harvey and Howes<sup>18</sup> have shown that such a diet causes accelerated fibroblastic proliferation. Without adequate building stores repair cannot take place.

A protein deficiency is of course not the only mechanism resulting in wound disruption. Sokolov<sup>19</sup> and Lanman and Ingalls<sup>20</sup> have shown that a vitamin C deficiency is also an important biologic factor in this complication. These two nutritional disturbances are frequently found in patients who come for operations for gastric ulcer and cancer, duodenal ulcer, and biliary tract disease. That plasma may be employed to restore depleted protein stores was indicated in the experiments in which we gave large amounts of plasma, as much as 2,400 cc. during a two-week period, to hypoproteinemic dogs that had been on a low protein diet for some days. The amount of plasma which we administered intravenously was more than six times the calculated plasma volume of the animal, but the plasma protein concentration never exceeded the original normal level for the dog. With the restoration of a normal serum protein concentration and, very likely, a more nearly normal store of tissue protein, the wounds promptly healed. Addis,<sup>3</sup> and Holman, Mahoney and Whipple<sup>21</sup> have shown that plasma protein can be utilized to replenish the depleted stores of tissue protein, and it is this purpose we believe that the excess protein, we injected, fulfilled.

When all the local factors favoring wound disruption are controlled, there will remain wounds whose failure to heal must be due to more widely acting causes such as hypoproteinemia and a reduction in "labile protein" stores, and deficiencies in important accessory foodstuffs.

*Protein and Its Influence in Preventing Visceral Injury.*—In a study of the protective action of oxygen against liver injury, when certain hepatotoxic anesthetics were employed, our attention was directed to the relation of the dietary regimen to the susceptibility of the liver to damage by these same agents. That a diet high in carbohydrate is protective and that a diet high in fat induces maximal susceptibility of the hepatic cells when the liver is exposed to chloroform, has been repeatedly confirmed since the original reports by Opie and Alford.<sup>22</sup> Experiments which Goldschmidt, Vars and I<sup>23</sup> have reported strongly suggest that glycogen *per se* does not protect the liver from the injurious effects of chloroform. Chemical analyses of the livers of animals following various diets, which were considered adequate and where feeding was prolonged, together with histologic evidence of changes in the cytology of the liver cells, have provided data which must lead to a realignment of our concept of the mechanism by which diet protects the liver or increases its susceptibility. It furthermore may, by inference, lead to certain conclusions on the effect of diet on regeneration.



## HYPOPROTEINEMIA

The data which Goldschmidt, Vars and I<sup>23</sup> obtained conclusively demonstrated that, regardless of the reasons for the toxic action of chloroform upon the cells of the liver, the incidence and degree of injury increases with increases in the concentration of lipid in the liver. The data reveal no evidence that the level of hepatic glycogen *per se*, at the time of anesthesia, influences the toxic action of chloroform.

The hypothesis which assumes that glycogen *per se* is effective in protecting the liver against the action of chloroform received no support from our experiments. The data on the incidence and severity of damage to the liver with high and low contents of glycogen were essentially the same where the content of lipid was similar. There can be no doubt but that the susceptibility of the liver to injury by chloroform is markedly enhanced by the presence of small increments of fat.

On the other hand, when animals had been fed diets with a relatively high or low content of protein in the rations, and where the lipid concentration was similar, a striking protection was observed in the rats which had been provided 17 per cent or more of their total calorific value from protein. The significant difference is to be found in the severity of the cellular changes, for in the high protein group areas of necrosis in the liver were found in but 41 per cent of the rats, while in the low protein group extensive necrosis was present in 88 per cent of the rats. Although a high protein diet did not markedly influence the total incidence of hepatic injury, it decidedly reduced the degree of injury. The protective action of protein revealed itself even in animals with a high concentration of hepatic lipid and a low concentration of hepatic glycogen. The incidence of hepatic injury in starved rats was compared with that which was found in fed animals with the same initial hepatic fatty acid concentration. The extent and severity of the damage to the liver in the starved animals was almost maximal and nearly as great as that which we had observed in fed animals with approximately 50 per cent concentration of hepatic lipid.

That a high carbohydrate dietary regimen is efficacious in preventing liver injury is agreed to by every clinician who has administered such a diet in patients with hepatic disease. It would seem that the explanation of its action must lie in some concomitant effect produced by large deposits of hepatic glycogen. Rosenfeld<sup>24</sup> has found that under many conditions of the body, depletion of hepatic glycogen is followed by an increase in fat in that organ and vice versa. Opie and Alford<sup>22</sup> suggested that the necrosis produced by chloroform, phosphorus and similar substances is perhaps the anatomic expression of advanced disintegration of body protein. Carbohydrate may, therefore, also be of value in limiting the necrosis due to these agents, by exerting its recognized function of sparing body protein.

The comparative protective value to the liver of foodstuffs against necrotizing anesthetics resolves itself, therefore, into the positive action of dietary protein versus the increased susceptibility to injury with increments in the hepatic lipid. In contrast to the indirect protection afforded by carbo-

hydrate the protection afforded by protein would seem to be a direct one, perhaps related to some intrinsic value of the protein itself.

The data which we have collected have led us to postulate that a liver high in lipid content and low in protein is maximally susceptible to injury; a liver low in fat and high in protein is maximally protected from injury. Carbohydrate is advantageous only if, during its deposition in the liver, fat is displaced and if, as a result of an adequate store of hepatic glycogen, hepatic protein is spared.

Protein stored or elaborated into the body tissues may serve to protect the hepatic cells or to offer protein for regeneration should damage occur. The increased susceptibility of the starved animal is in our opinion chiefly a matter of depletion of its easily mobilizable protein stores.

Even so great an advocate of the carbohydrate protective concept as George Whipple<sup>25</sup> has recently confirmed our findings, and his associates<sup>26</sup> have extended them, for they have shown that a high protein dietary regimen protects the liver from the necrotizing effects of arsphenamine. It is highly likely that a protein deficiency in the organism, frequent in surgical patients, either with or without hypoproteinemia, may lead to hepatic and other visceral injury following the use of a wide variety of hepatotoxic agents.

The evidence which we have brought forth, fortified by the recent investigations of Miller and Whipple,<sup>25</sup> and his associates, Messinger and Hawkins,<sup>26</sup> makes it highly probable that a carbohydrate-protein diet should be given in the future before operation wherever possible, and begun again after operation as soon as the gastro-intestinal tract will tolerate food.

Johnson, Vars, Zintel and I<sup>27</sup> have found that in the dog with a high lipid content in the liver, a diet consisting of approximately 72 per cent of the calories as carbohydrate, and 28 per cent as protein, was twice as efficient in reducing the concentration of hepatic lipid as carbohydrate alone given in the same number of calories per kilogram per day. If minimal visceral injury is to be conditioned and repair facilitated, an adequate amount of protein must be added to an otherwise satisfactory caloric intake.

#### CONCLUSIONS

An attempt has been made to demonstrate that a protein deficiency may be of serious significance in surgical patients. The reduction of the plasma protein, both in concentration and total amounts, frequently is associated with a reduction in the amount of protein stored in certain viscera. A reduction in the concentration and total amounts of the plasma protein as well as the so-called "labile stores" of body protein may result in the failure of a newly formed gastro-enteric or intestinal anastomosis to function normally, to impairment of normal fibroblastic proliferation and to increased susceptibility of certain viscera to damage by hepatotoxic agents.

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## FLUID AND NUTRITIONAL MAINTENANCE BY THE USE OF AN INTESTINAL TUBE \*

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THE MAINTENANCE of the fluid balance and nutritional state of a patient with an obstruction of the alimentary canal is made easier by the use of a rubber tube, but the manner of its use is diametrically opposite in the upper as compared to the lower end of the tract. When the esophagus or the pylorus is blocked, the tube may be surgically inserted below the lesion. Food is injected through it and the residue is passed by rectum. When the small intestine or colon is obstructed, the tube may be swallowed to the point of obstruction and through it may be withdrawn the residue of food which is eaten normally. Thus the nutritional problem in the high obstruction is to prepare a food that can be injected and will be tolerated by the digestive tract; in the low obstruction it is to find an adequate diet the residue of which can be withdrawn.

The problem is relatively simple in esophageal cases because the stomach tolerates a wide difference in the composition of its contents, and long experience with gastrostomies has shown that any feeding containing a reasonable balance of protein, fat, carbohydrate, vitamin, minerals and water will meet the requirement.

Jejunal feeding after the surgical relief of a pyloric obstruction is, however, a far more debatable subject: First, because it is not generally thought to be advisable; second, because the technic is less standardized; and, third, because the jejunum is a far more sensitive organ than the stomach and less tolerant of random feeding mixtures.

No one, to my knowledge, advocates jejunal feeding after every gastroenterostomy. On the other hand, patients with slowly stenosing pyloric lesions whose emaciation has become marked, before an episode of intractable vomiting brings them to the surgeon, present such a grave nutritional problem that one is impressed more by the fact that standard measures are so often successful than by the frequency with which failure results. The problem is intensified, moreover, by the common practice of keeping the stomach empty for another three or four days after operation. During this period, water, salt, and carbohydrates are given in abundance intravenously, but the protein intake is limited to that which can be administered by transfusion; and the total caloric intake rarely attains 800 per day. The work of Ravdin and his associates,<sup>1</sup> in particular, has, during the last few years, laid ample emphasis on the importance to the surgical patient of the protein intake. Not only does hypoproteinemia adversely affect wound healing, but

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many of the mechanical difficulties encountered at the gastro-enterostomy stoma, which were formerly thought to be due to errors in surgical technic, have been shown by them to be due to hypoproteinemic edema of the traumatized intestinal wall. The preceding speakers in this symposium have amply clarified the rôle which slight imbalance in the salt, fluid and protein intake can play in complicating the convalescence of these patients.

Noting the frequent use of intravenous infusion to sustain postoperative patients, and being impressed by the fact that the entire absorbing surface of the small intestine was available for tube feeding after a gastro-enterostomy, Andresen,<sup>2</sup> in 1918, began the practice of passing a Jutte tube into the jejunum at operation. The procedure, however, fell into disuse as appreciation of the im-

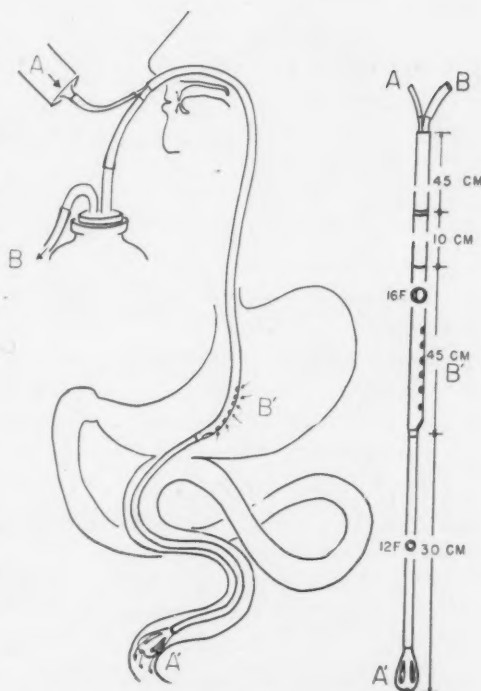


FIG. 1.—The gastro-enterostomy tube in place: (A) route of injection of nutrient solutions; (A') point of emergence of the solution; (B) attachment for the application of suction; (B') points from which contents are aspirated. (Reproduced from J.A.M.A., 112, 2414, June, 1939.)

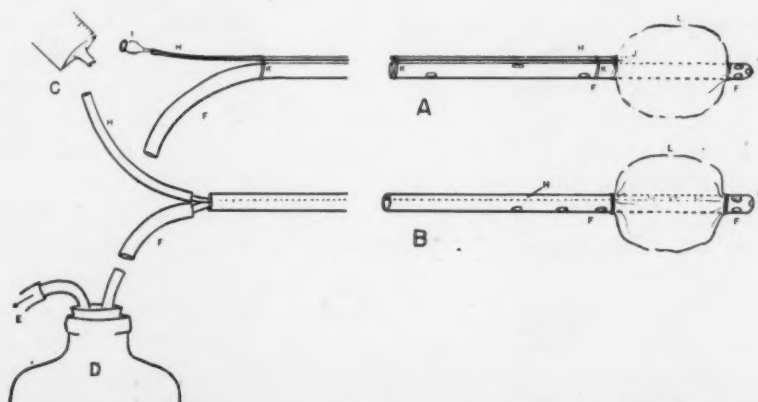


FIG. 2.—Small intestinal tubes arranged in a manner suitable for the treatment of acute intestinal obstruction. (A) Constructed with two tubes fastened together; (B) constructed with one double-lumened tube; (C) 50 cc. glass syringe for filling the balloon (L); (D) bottle for collecting and measuring the aspirated intestinal contents; (E) tube leading to syphon bottles for maintaining suction; (F) passage through which intestinal contents flows; (G) any type of metal or rubber tip small enough to pass through the nose; (H) passage conducting air to the balloon; (I) hub of a No. 16-gauge needle to receive the syringe nipple; (J) a portion of the needle barrel inserted in the small tubing to facilitate tying on the balloon; (K) silk threads loosely tying the tubes together; (L) about two and one-half inches of rubber condom tied on with silk to form a balloon that can easily accommodate 30 cc. of air. (Reproduced from Penn. State Med. Jour., 42, 890, May, 1939.)



portance of an empty stomach after gastric surgery gained ground, and tubes, if passed at all, were used for aspiration purposes only. Rawson and I<sup>3</sup> have met both requirements by using a double-lumened tube, one passage for gastric suction, one for jejunal feeding (Fig. 1). The surgeon passes the tip through the stoma on completion of the anastomosis and 12 hours later jejunal feeding is begun. An extremely cachectic individual, dying after such a tube had traversed the suture line for 13 days, showed no gross or microscopic evidence of damage to the mucosa. The feeding can be given by drip, by the electrically controlled pump of Stengel and Vars,<sup>4</sup> or by intermittent injection of 20 cc. volumes with a syringe. The last method gives a slight stimulus to peristalsis which starts the distribution of the fluid down stream.

The feeding mixture must be prepared with the following points in mind, *viz.*: (a) The normal fasting jejunal contents are hypotonic;<sup>5</sup> (b) the maximal glucose concentration that will normally enter the duodenum from the stomach is 15 per cent;<sup>6</sup> (c) the maximal sugar concentration obtainable from the jejunum after glucose ingestion is 6 per cent;<sup>7</sup> and, finally, (d) hyperperistalsis is produced by the introduction into the intestine of any glucose solution greatly in excess of these values.<sup>7</sup> Glucose has been taken here as an example of the end-result of digestion. In general, the same is true of amino-acids and fatty acids. In a word, it seems desirable to predigest the food to avoid the risk of there being inadequate ferments for digestion in the sick patient, but the farther the process is carried the more irritant becomes the product, unless the concentration is correspondingly reduced. Thus, the more the predigestion the harder it becomes to increase the calories though it is possible that more of what is given is absorbed. That this is not an insurmountable problem is indicated by the very considerable success experienced by Stengel and Ravdin<sup>8</sup> in elevating the serum protein level of these patients by the jejunal feeding of a casein hydrolysate. This is not yet on the market, however, and for the present acidified skim milk, incubated with commercial pepsin and fortified with 6 Gm. of dextrose per 100 cc., and neutralized by the addition of sodium bicarbonate, gives a relatively high protein, high carbohydrate, and low fat feeding, that supplies about 1,500 calories in 2.5 liters. To this should be added, per day, 1 cc. of viosterol in fish liver oil, 20 mg. of thiamin chloride, 50 mg. of nicotinic acid, and 100 mg. of ascorbic acid. The food value of the mixture can be increased as the patient's tolerance permits.

This procedure, of postgastro-enterostomy jejunal feeding, has not yet been carried out in enough patients to allow the presentation of statistically valid evidence as to its worth in comparison with standard methods. Sufficient experience has been had with it, however, to warrant the statement that it is both practicable and practical.

A typical case is one from the series of Stengel and Ravdin:

**Case Report.**—B. K., male, age 57, was admitted to the hospital, with a history of 15 years of "heartburn" and "bloating," especially after heavy meals. He habitually obtained relief by inducing vomiting or by taking sodium bicarbonate. Constipation was

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persistently present. Six months before admission he lost his appetite. Though his weight loss was 20 pounds during the last four weeks before his admission, he stated that frank pain was of less than 24 hours' duration. Vomiting had become spontaneous and frequent. Examination revealed generalized upper abdominal tenderness without rigidity. The initial impression of a duodenal ulcer was confirmed at operation but evidence of a previous small perforation was presented by the fibrinous exudate over the surface of the stomach and the firm adherence of small bowel to the anterior surface of the duodenum. A posterior gastrojejunostomy was performed, and before closing the abdomen a double-lumened gastro-enterostomy tube was passed through the stomach into the jejunum.

Before operation, he was dehydrated, and showed a plasma chloride level of 95.2 m.eq./L., and a plasma protein of 7.1 Gm. per 100 cc. Gastric suction was instituted at once, and jejunal feeding was started on the second postoperative day. In spite of a transfusion both before and after operation, his plasma protein level had dropped to 5.3 Gm. per 100 cc. by that time. During the next week he received no further transfusions, all his fluid being given by mouth or into the jejunum. That which was taken by mouth was, in the main, drained out again promptly, serving chiefly to keep the mouth and throat clean and the stomach washed clear of mucus. On the first day of jejunal feeding, the volume given was limited to 680 cc. Thereafter, it varied from 1,794 to 2,274 cc. per day. At the end of this week the plasma protein was 6.7 Gm. per 100 cc. The feeding mixture used in this instance was an experimental casein hydrolysate being investigated by Doctors Ravdin and Stengel. It contained 5 per cent of glucose as well as the split products of casein digestion. From the standpoint of technic, however, it exemplifies the simplicity of a method that promptly makes available to the physician the normal route of absorption in a patient the nature of whose disease would otherwise force one to the use of more artificial procedures.

Obstructions below the pylorus, involving the small intestine and colon, present a totally different problem from the nutritional standpoint, and here the use of the tube is reversed (Fig. 2). Its primary purpose is to decompress the distended intestine and to tide the patient over an acute crisis. If the obstruction is of such a nature that operation is necessary, the patient must be properly prepared for surgery from the fluid, electrolyte and serum protein standpoint; if the obstruction is of inflammatory origin, he must be kept in a good state of nutrition during the week or two which may pass before his bowels move.<sup>9</sup> There are two chief points of importance to be considered here: First, to appreciate the extent to which his electrolyte reserves are being depleted by the constant drainage of his intestinal contents; second, to supply him with a diet that he can eat in spite of an inlying tube in his nose and throat, and that will yield a residue which can be drawn back through the tube.

The most important element lost in the drainage from points below the duodenum and high jejunum is sodium chloride. Too much has been said already about the causes and results of salt loss and the technic of its replacement to require amplification here. Maddock<sup>10</sup> has devised a formula for calculating the immediate salt replacement required when the patient is in a critical state. It is a great help during the period of maintenance, however, to use the volume of drainage as the basis of calculation for salt replacement because it is so obviously quick and convenient. Luckily, the concentration of salt loss is remarkably constant in the face of even widely varying amounts

of salt and fluid administered, without regard to the route of administration.<sup>11</sup> Figure 3 shows that about 0.6 Gm. per 100 cc. not only represented the average of 67 determinations but it is apparent that little deviation from the average took place and that little variation occurred when collections were made from different levels in the bowel. Figure 4 shows the range of variation in an individual case. From this, the convenient conclusion may be drawn that sodium chloride, grains x, given in capsules each time the patient drinks 100 cc. of water will come very close to maintaining an intake of the same salt concentration as is present in the output by drainage.

## SODIUM CHLORIDE LOSS IN DRAINAGE FROM OBSTRUCTED INTESTINE

5 PATIENTS

(Gm./100 cc.)

	Analyses	Highest	Lowest	Average
Stomach, duodenum and jejunum.....	10	0.68	0.37	0.49
Ileum.....	49	0.81	0.38	0.61
Cecum.....	8	0.65	0.51	0.59
Total.....	67			0.58

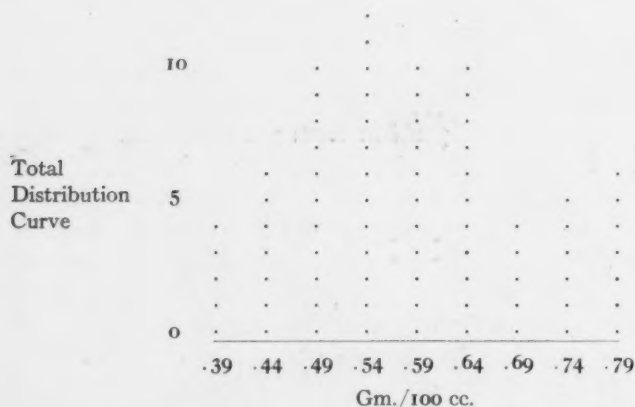


FIG. 3.—Concentration of sodium chloride lost by intestinal drainage.

Another bit of good fortune is apparent in considering the food requirement. The importance of a low residue has been stressed. Since the patient with intestinal obstruction may be in as great need of serum proteins as the patient with pyloric obstruction and for much the same reasons, it is fortunate that a high protein diet and a low residue diet are identical. The best study of dietary residue in this regard is still that of Hosoi, Alvarez and Mann.<sup>12</sup>

When a patient with a low obstruction is treated by the passage of a small intestinal tube, strained fluids should be started at once provided that salt is given as described. While the tube is in the stomach this constitutes gastric lavage. As soon as it traverses the duodenum the fluid begins to

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contribute to his maintenance. When the tube is progressing down the jejunum strained soup, tea, coffee, melba toast, puffed rice and clear jellies are cautiously tried. To this may be added zwieback, Holland rusks, boiled rice, cream cheese, well cooked eggs and finally strained cereal, chicken and lean beef and lamb. Noer and Johnson<sup>13</sup> have reported a very satisfactory dietary. On such a regimen the patient should be able to take 1,500 to 1,800 calories daily for two to three weeks in spite of complete obstruction if the nasal and throat irritation from the tube can be combated for that long a period.

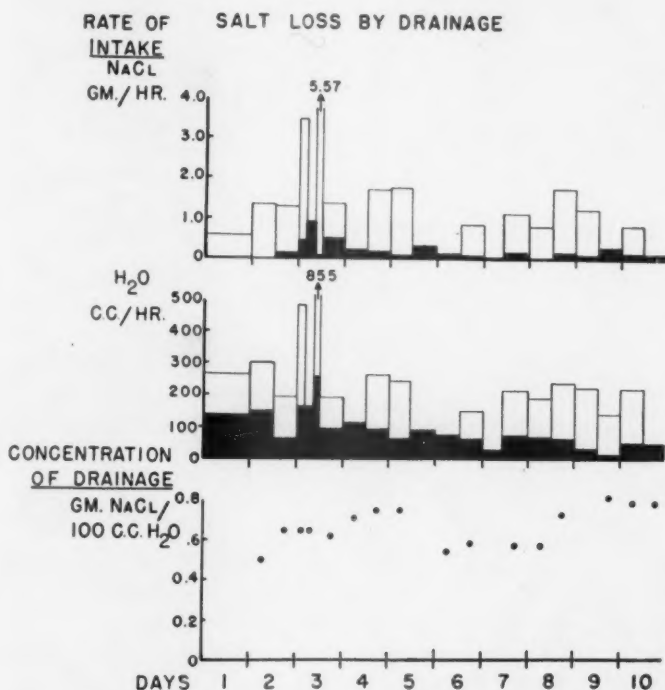


FIG. 4.—Case E. B.: A postsplenectomy obstruction of the small intestine was constantly decompressed by aspiration of the small intestinal contents above the point of obstruction for ten days. Because of technical difficulties he could not be controlled satisfactorily and, therefore, required salt by mouth (black) and parenterally (clear) at totally irregular intervals. In spite of this, the salt concentration in the drainage did not vary more than 0.15 per cent from the usual average level of 0.6 Gm. per 100 cc.

Under these circumstances his vitamin requirement may be met by the use of viosterol capsules, autolized brewer's yeast and orange juice in adequate amounts daily.

A typical case so treated is appended:

**Case Report.**—J. R.,\* white, male, age 58, steamfitter, was in good health till 2:45 P.M. when he was seized with a diffuse cramp-like pain in the abdomen while he was at work in the hospital. In retrospect, he afterwards recalled some vague abdominal distress

\* Patient of Dr. E. L. Eliason.

during the preceding 48 hours but he had paid no attention to it. Within an hour, the pain had localized in his right lower quadrant; he began to vomit, and in less than two hours from the onset, operation had revealed a ruptured appendix with seropurulent fluid free in the peritoneal cavity. The wound was drained and he was given sulfanilamide. At the end of 24 hours, a Wangenstein tube was used because of distention. This was

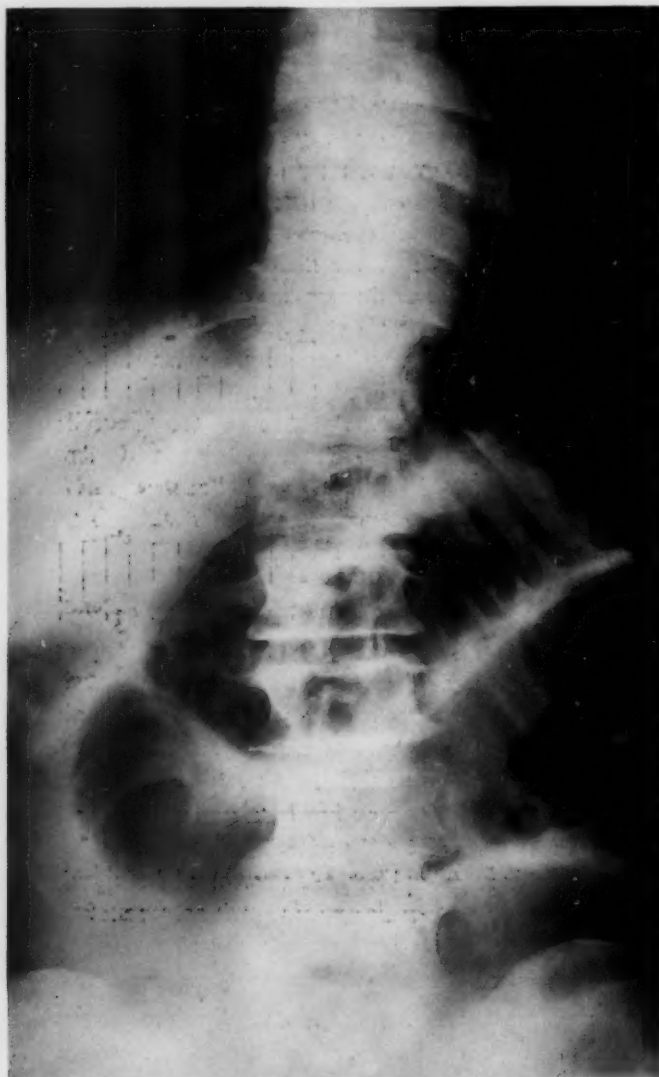


FIG. 5.—Case J. R.: Roentgenographic evidence of small intestinal obstruction.

removed on the second day, and for the next six days the patient took liquids by mouth, but because of ill-defined distress on eating it was necessary to supplement this by intravenous infusions of glucose and salt solution. Peristalsis was present but was hypoactive till the sixth postoperative day when it became hyperactive and the patient vomited. This was repeated on the eighth day. The Wangenstein tube was reinstated but was again



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removed on the ninth day because the patient was comfortable. On the eleventh day vomiting recurred, accompanied by distention. This rapidly increased and a gastrointestinal consultation was asked for on the thirteenth day. Although the patient passed one puff of flatus that day the clinical and roentgenologic evidence was of a mid small intestinal obstruction (Fig. 5). A long intestinal tube was passed into the stomach by Dr. Richard Warren, but for over two days neither he nor I could advance it into the small intestine. During that time it kept the stomach deflated and some decompression was accomplished by removing the reflux of small intestinal contents. The advisability



FIG. 6.—Case J. R.: Roentgenogram showing a tube descending the small intestine. The patient was taking fluid, salt, and food by mouth. Decompression was not yet complete.

of performing an enterostomy was repeatedly discussed but on the third day Doctor Warren successfully introduced the tube into the jejunum and from then on decompression progressed rapidly. On the seventeenth day, the location of the obstruction was demonstrable by the injection of barium down the tube under the fluoroscopic guidance. One isolated segment of ileum remained out of reach of the tube for a time (Fig. 6) but in the course of a few days the tip entered and emptied it also. On the twenty-first day a little feces was passed but it was not until the twenty-third day that the tube could be clamped off entirely. It was removed on the twenty-fifth day and convalescence continued normally with no subsequent evidence of obstructive phenomena in the year that has elapsed.

From the sixteenth to the twenty-fourth day the patient was, for all practical purposes, completely obstructed, though toward the last of this period he began to pass small quantities of feces per rectum. Intravenous infusions were administered occasionally but, from the nutritional standpoint, he derived most of his fluid, salt and calories from what he took by mouth. His nutrition was good when his appendix ruptured. During the first two weeks after operation he received far less than his basal caloric requirement. When intubated he was dehydrated, his serum chlorides were 89 m.eq./L. and his serum protein 6.8 Gm. per 100 cc. Three days later he was hydrated, his serum chlorides were 96.6 m.eq./L. and his serum proteins 5.9 Gm. per 100 cc. It is doubtful if the change in percentage concentration means anything more than increased blood volume. By mouth he received a diet of 1,200 calories in three meals to be chosen from the foods listed earlier. These foods were well salted and in addition he received salt in capsules as indicated. Two blood transfusions were given during his hospital stay. His vitamin requirement was adequate. He did not always eat the amount of food offered and on some occasions he vomited a portion of what he had eaten. Although this case could not be conducted as a balance experiment, it was the feeling of the staff that his state of nutrition was good when the obstruction disappeared. In support of this opinion was the fact that he was sitting up beside his Wangenstein bottles while still obstructed and was well enough to go home the day his tube was removed.

## CONCLUSIONS

In the presence of high obstructions in the alimentary canal a tube may be placed by surgical means in such a position that food may be introduced into the tract below the obstructing lesion. When this food is placed in the stomach a wide leeway in its preparation is permissible. When the food is placed in the small intestine it must be very carefully prepared so that it will not be irritant from too little digestion on the one hand or from too much digestion on the other.

In the presence of low obstructions the tube is passed to the obstruction itself and is then used to recover the residue of food eaten normally. The point of importance under these circumstances is to supply those foods most needed by the patient and at the same time to avoid all foods the residue of which cannot be drawn back through ten feet of tubing.

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## PARENTERAL REPLACEMENT OF PROTEIN WITH THE AMINO-ACIDS OF HYDROLYZED CASEIN \*

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PARENTERAL REPLACEMENT of protein has become recognized as an important therapeutic need only during the past decade. This has been due largely to an increasing realization of the frequency and seriousness of hypoproteinemia in a variety of patients and in the apparent inability of the body to always correct this deficiency spontaneously. The problem is made more serious by the fact that transfusions frequently fail to correct the deficiency and for many other reasons; there is, in addition, a growing appreciation that protein needs other than those for the synthesis of serum protein may be important in many patients nutritionally depleted and unable to take and absorb nourishment adequately by mouth.

The possibility of supplying protein needs parenterally with amino-acids has been suggested from time to time, particularly by Rose,<sup>1</sup> in 1934, and was achieved experimentally as early as 1913 by Henrique and Andersen.<sup>2</sup> In the human, amino-acids were injected intravenously for purposes of protein alimentation for the first time in this clinic;<sup>3</sup> the amino-acid preparation used at that time was a mixture obtained by acid hydrolysis of casein, fortified with tryptophane which is destroyed during digestion by acids. Evidence of utilization, experimentally and clinically, as well as therapeutic effects in patients, was observed.<sup>3</sup> The necessity of adding tryptophane was, however, a disadvantage because of its cost.

The present observations are concerned with the injection of an enzymatic hydrolysate of casein,<sup>†</sup> containing *all* amino-acids present in casein, including tryptophane, and capable of maintaining nitrogen balance and promoting normal growth in rats.<sup>4</sup> This preparation has the power of provoking serum albumin restoration in experimentally produced acute hypoproteinemia.<sup>5</sup> Clinical observations in children have already been reported with this enzymatic product by Shohl, Butler, Blackfan and MacLachlan,<sup>6</sup> and by Farr and MacFayden.<sup>7</sup> Both of these groups of observers presented data indicating that the injected material was utilized. Although the former workers noted severe reactions (chills and fever) following the injection in several babies, the latter have injected large amounts without such reactions.<sup>8</sup> Undoubtedly, this difference was due to differences in the manner of preparation of the solutions for intravenous use.

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† This material has been generously supplied by Mead Johnson and Company, Evansville, Indiana.

The enzymatic hydrolysate, though a complete mixture of amino-acids, is, I am told, not as easy to prepare as the acid hydrolysate because of numerous technical difficulties. Unlike the latter, the former product is not completely hydrolyzed, only two-thirds being in the form of amino-acids, the remaining third being in a more complex form, presumably dipeptides. It is, however, not anaphylactogenic for guinea-pigs; moreover, the incompleteness of the hydrolysis is apparently of no biologic significance. This enzymatic preparation of casein (called 92-Z) was used in all of the observations reported herein. It should be mentioned, however, that successive batches of this product have been used, each of which has represented improvements in the method of manufacture as shown by easier solubility and less tendency toward reaction when injected intravenously, even when given at a faster rate than earlier products.

*Method of Administration.*—As received, the product is a dry, impalpable powder which is made up as a 10 per cent solution and heated to 90° C. For complete sterilization the solution is passed through a Seitz (EK) filter and 100 cc. amounts poured into flasks containing 400 cc. of sterile 10 per cent glucose; the mixture is then injected intravenously during one hour. Thus, in eight hours of continuous venoclysis (or two four-hour periods) 4,000 cc. can be injected—containing 1,600 calories and 80 Gm. of protein as amino-acids. Adequate electrolyte is also added, ordinarily as concentrated Ringer's solution—equivalent to 10 Gm. of salt per day. The nitrogen concentration of the 10 per cent solution is 1.2 Gm. per cent—so that when 4,000 cc. are administered the patient receives 9.6 Gm. of nitrogen. This is equivalent to the nitrogen in 3,000 Gm. (nearly  $\frac{3}{4}$  lb.) of lean beef.

For injection the ordinary infusion flask has been used, the rate of flow being measured by the drops falling through an interpolated sealed glass trap. All connections were of glass and only stainless steel needles were used.

*Difficulties Encountered.*—Most of the earlier difficulties have disappeared with successive improvements in the manufacture of the hydrolyzed casein. The solubility has increased, so that precipitation of the solutions is no longer encountered. Obviously, a perfectly clear solution must be maintained before the material can be administered intravenously. Another difficulty has been the phlebitis induced when long periods of venoclysis were required. It has been my impression that the more recent preparations of hydrolyzed casein have shown less tendency toward thrombosis. This tendency, however, is not very great with the dilute (2 per cent) solutions.

The most serious difficulty has proved to be the occurrence of occasional reactions, similar to those reported by Shohl, *et al.*<sup>6</sup> Many patients had none even after two weeks of daily injections. In a few cases the reactions were undoubtedly due to the rapidity of injection. Thus, in Case 4, on March 24, 1939, 2,250 cc. of a 10 per cent glucose solution, containing 2 per cent of product 92-Z, was administered in five hours without reaction; later in the day, 1,500 cc. of the same solution was administered in two hours, and was followed by a chill and a temperature rise of 3° C. Whatever the cause of



reactions, there has been a complete absence, thus far, with the more recently received material. Indeed, the latest product (No. 143, which has already been brought into solution by the manufacturer) has been injected into three patients at a speed twice as fast as that already mentioned. Thus, 1,000 cc., containing 10 per cent glucose,  $2\frac{1}{2}$  per cent hydrolyzed casein, and 0.45 per cent NaCl, was given in one hour without reaction. In spite of the rapidity of the injection less than 0.1 Gm. of amino-acids of the 25 Gm. given appeared in the urine during the ensuing three hours. I believe that untoward reactions are due to one or more factors connected either with the manufacture of the hydrolyzed casein, with its method of solution and preparation for intravenous use, or with the technic of administration itself. These factors appear to be almost if not completely solved with the most recent product; only further experience will tell.

It must, of course, be admitted that uniformity in the composition of the amino-acid mixture is highly desirable if not essential. Whether such a uniformity can be or actually has been achieved is still incompletely answered and awaits further experience. Nevertheless, the preparation now available for experimental use has been administered to 35 patients, and data of much interest and great promise have been accumulated.

*Clinical and Metabolic Observations.*—The mixture of glucose, amino-acids and electrolyte described above was administered to 35 adults as their sole source of fluid and food; the period of treatment varied from one to 23 days and averaged over ten days. The total daily dose varied somewhat, but in most cases a maximum amount of 80 Gm. of 92-Z was given; this averaged between 1 and 2 Gm. per Kg. per day, dependent upon the body weight of the patient. As already mentioned, 80 Gm. of the hydrolyzed casein contains 9.6 Gm. of nitrogen. In 20 patients, nitrogen balance studies were carried out; complete collections of urine, feces and vomitus were analyzed for total nitrogen by the Kjeldahl method. Serum proteins were also determined in this way. The serum was fractionated by Howe's method. Of the following eight representative cases, the first two are normal controls, the next two preoperative and the last four postoperative patients.

#### REPORTS OF EIGHT REPRESENTATIVE CASES

**Case 1.**—Hosp. No. D-7721: P. W., Negro, male, age 55, was admitted, November 1, 1939, to the Homer Phillips Hospital. He was an asthmatic, and had been a patient many times previously with the complaint of respiratory distress. This time he complained more especially of epigastric pain and vomiting and had lost 20 pounds in weight. Examinations including cholecystogram and gastro-intestinal roentgenologic series were negative. All laboratory tests were negative; the serum protein was 7.01 Gm. per cent, albumin 4.2 Gm. per cent. Intravenous alimentation, with complete gastro-intestinal rest, was suggested and he accepted this regimen. During 15 days he took nothing but a little cracked ice by mouth, and was given each day 3,000 cc. of 10 per cent glucose containing the equivalent of 1,000 cc. of Ringer's solution, i.e., two ampules of concentrated Ringer's (each sufficient for 500 cc.). After three days, a solution containing 60 Gm. of amino-acids (92-Z) was added to the glucose (Fig. 1). Only one reaction occurred during the intravenous therapy on the fifteenth day, when the patient had a slight chill but exhibited

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no elevation of temperature. Subjectively the procedure was well tolerated; the patient's epigastric pain disappeared completely and when he was put on a regular diet it did not recur. He left the hospital asymptomatic and returned three months later with a request for a repetition of the experience.

**Case 2.**—Hosp. No. D-5541: Z. C., Negro, male, age 65, was admitted, November 5, 1939, to Homer Phillips Hospital. He was a frequent patient in the hospital, the diagnosis each time being bronchial asthma and hypertension; the electrocardiogram showed advanced myocardial damage. He had lost some weight and complained of difficulty in swallowing although all examinations including a cholecystogram and gastro-intestinal roentgenologic series were normal. Laboratory tests were all normal, the serum protein was 7.2 Gm. per cent, albumin 3.3 Gm. per cent. A period of complete gastro-intestinal

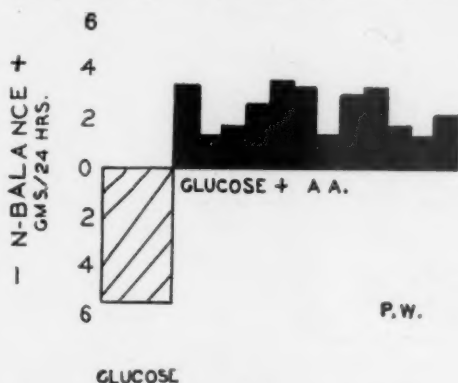


FIG. 1.

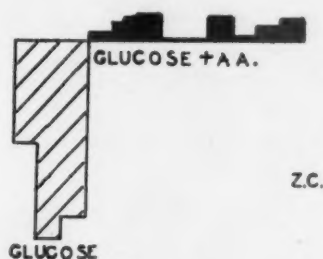


FIG. 2.

FIG. 1.—Case 1, and FIG. 2.—Case 2: In both cases represented above, the gastro-intestinal tract was normal (see Case Reports). Note, in both, the immediate achievement of positive nitrogen balance when amino-acids were added to the intravenous glucose. The cross-hatched columns represent the nitrogen output during three days, during which 3,000 cc. of 10 per cent glucose was injected daily. The solid black represents the period during which 60 Gm. of hydrolyzed casein (7.2 Gm. N.) was added daily. The metabolic study in Case 1 lasted 15 days, in Case 2, 12 days.

rest was suggested to him, which he accepted. For 12 days he was given only cracked ice by mouth and 3,000 cc. of 10 per cent glucose plus Ringer's solution for three days, and then amino-acids were added (Fig. 2) as described in Case 1. He had no reactions whatever during the experiment and complained of no hunger. When he was returned to a regular diet he was able to eat better and left the hospital much improved.

**Case 3.**—Hosp. No. 73309: G. A. H., white, male, age 48, was admitted, March 10, 1939, to Barnes Hospital. He had had several abdominal operations elsewhere for appendicitis, intestinal obstruction and ventral hernia, and presented a small intestinal fistula of four months' duration which developed following the last celiotomy. He had lost 40 pounds in weight during his illness. The wound was treated conservatively for several weeks when it was finally decided to close it surgically. This was done, April 5, 1939; it required resection of much diseased small intestine on either side of the fistula, but was successful. Preparatory to operation he was put on "nothing by mouth" and given intravenous injections of glucose, Ringer's solution and amino-acids, the amounts as indicated in the legend under Figure 3; vitamins C<sub>1</sub> and B<sub>1</sub> were also injected. It is interesting to note that during the period of gastro-intestinal rest the flow of intestinal contents from the fistula was active, the total nitrogen from this source varying between 0.2 and 0.9 Gm. per 24 hours. This patient had two reactions during the injection of the amino-acids but in each case it was associated with a rapid rate of flow and was transient. The serum protein was 6.5 Gm. per cent, albumin 4.2 Gm. per cent. Following his discharge from the hospital the patient regained his loss of weight and has remained well.

**Case 4.**—Hosp. No. 81491: J. B., white, male, age 37, was admitted, October 20, 1939, to Barnes Hospital. He had become ill three months before with severe diarrhea and cramps which resulted in a 51 pound weight loss. On admission, he was emaciated and miserable; in spite of various oral regimens he continued to have three to ten stools a day and much abdominal pain. His serum protein remained low, 5.1 Gm. per cent, albumin 3.0 Gm. per cent. A diagnosis of regional ileitis was made, largely with the aid of a gastro-intestinal roentgenologic series, and operation was advised. This was carried out several months later, after he had gained 30 pounds in weight and had a normal serum protein. The lesion at operation proved to be characteristic of regional ileitis. On November 15, 1939, a period of intravenous alimentation was started; nothing was taken by mouth but cracked ice. The metabolic findings are recorded in Figure 4. The clinical response was pronounced; his pain disappeared, stools ceased, abdominal distention diminished, and general well-being improved remarkably. On the twelfth day of the experiment he was started on glucose and amino-acids by mouth, without any return of symp-

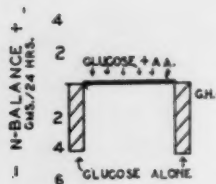


FIG. 3.

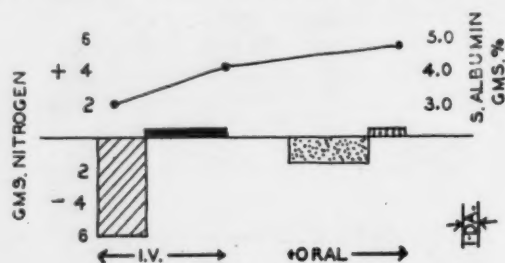


FIG. 4.

FIG. 3.—Case 3, and FIG. 4.—Case 4: These charts represent two preoperative cases (see Case Reports). Note, in both, the achievement of positive nitrogen balance during the periods in which hydrolyzed casein was added to the intravenous glucose (represented in solid black). In Case 3, on the first and sixth days (represented by the cross-hatched columns), 3,000 cc. of 10 per cent glucose was injected. On the second to fifth days, 50 Gm. of amino-acids (6.0 Gm. of N.) was added daily. In Case 4, on the first three days (represented by the cross-hatched columns), 3,000 cc. of 10 per cent glucose was injected daily; during the following five days, 60 Gm. (7.2 Gm. N.) of amino-acids was added. (The data on the ninth, tenth and eleventh days are omitted because of difficulties with the intravenous flow and loss of specimens.) Note the negative nitrogen balance during the next five days (represented by the dotted column) when the same amount of glucose and amino-acids was taken orally; this suggests the superiority of intravenous over oral administration. During the final two days, the dose of amino-acids was increased to 80 Gm. (9.6 Gm. N.), whereupon nitrogen balance was achieved. Note also in this case the increase in serum albumin from 3.0 to 4.6 Gm. per cent. The serum globulin remained unchanged at 2.1 Gm. per cent; as did the red cell count.

toms, and later was gradually put on a regular diet; upon this regimen he gained 30 pounds before being operated upon. It is of interest to note the increase in serum protein in this patient from 5.1 Gm. per cent, on November 15, 1939, to 6.7 Gm. per cent, three weeks later; the increase was all in the albumin fraction. No reactions whatever occurred during the intravenous therapy in this patient. His sense of hunger was definitely satisfied during the days in which he was receiving the amino-acids in contrast to its presence while receiving glucose alone. The metabolic studies in this patient were carried out with the cooperation of Dr. Cyril MacBryde to whom I am indebted for the data obtained.

**Case 5.**—Hosp. No. D-10914: B. P., Negro, male, age 46, was admitted, February 8, 1940, to the Homer Phillips Hospital. He was operated upon soon after admission for a perforated peptic ulcer, which was found on the posterior surface of the pylorus, and was closed. The lesion had been present for over 24 hours, and a definite peritonitis was present. Intravenous glucose and Ringer's solution were given for five days; during this time his clinical course was stormy and, as can be seen in Figure 5, a large amount of nitrogen appeared in the urine. On the sixth day, amino-acids were added to the glucose and continued for 11 days. The sudden improvement in the general condition of the patient was striking and coincided with the addition of the amino-acids. Of interest, too, was the increase in the serum albumin and globulin, the

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total serum protein changing from 6.11 Gm. per cent on February 10 to 7.4 Gm. per cent on February 27. That this change was not due to a concentration of the blood (decrease in plasma volume) was shown by the fact that the red cell count remained unchanged.

**Case 6.**—Hosp. No. D-12080: S. W., Negro, female, age 29, was admitted, March 14, 1940, to the Homer Phillips Hospital, and operated upon soon afterward for a strangulated umbilical hernia. The involved small intestine was gangrenous and a resection was carried out. During the first four postoperative days she received glucose and Ringer's solution alone, to which was added, during the next four days, 80 Gm. of hydrolyzed casein. Thereafter she was started on fluids by mouth and finally a regular diet. The patient weighed but 50 Kg., so that the amount of amino-acids she received was almost 2 Gm. per Kg. The clinical course was stormy for the first few days but improved remarkably with the onset of amino-acid injections. This was also evident, objectively, by a diminution of distention and the passage of gas and stool. It is important to note here, as in Case 5, the large urinary output of nitrogen in the postoperative period in spite of the administration of a large amount (1,600 calories) of glucose (Fig. 6). Laboratory tests were otherwise not notable; the serum protein was normal.

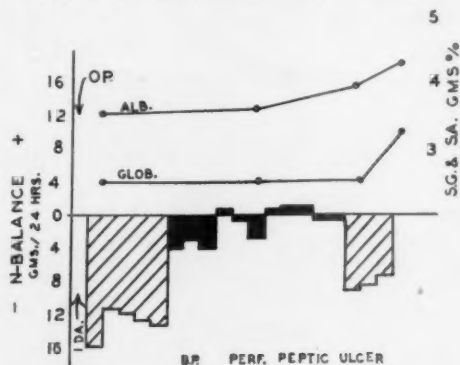


FIG. 5.

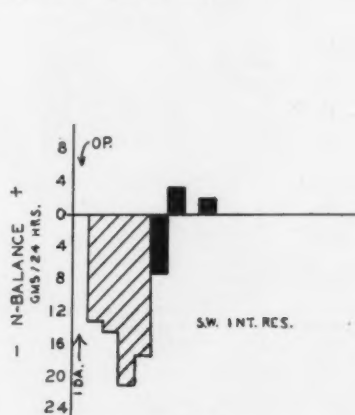


FIG. 6.

FIG. 5.—Case 5, and FIG. 6.—Case 6: These charts represent two postoperative cases (see Case Reports). Note the large output of nitrogen (12 to 20 Gm. per day) in both, in spite of the daily injection of 4,000 cc. of 10 per cent glucose (represented by the cross-hatched columns). The columns in solid black represent the addition of 80 Gm. (9.6 Gm. N.) of 92-Z to the glucose; note that nitrogen balance was achieved on several but not on all of these days. Note, too, the increase in serum albumin and globulin in Case 5.

**Case 7.**—Hosp. No. D-10954: J. H., Negro, male, age 73, was admitted, February 9, 1940, to the Homer Phillips Hospital. He was operated upon soon afterward and a large volvulus of the sigmoid was untwisted, replaced in the abdomen and the wound closed. Recovery was uneventful, particularly after the third day, coincident with the addition of hydrolyzed casein, of which he received 80 Gm. per day for 13 days together with 4,000 cc. of 10 per cent glucose and Ringer's solution. The period of intravenous therapy was especially long because of persistent distention which finally subsided with the passage of normal stools. Note the large output of urinary nitrogen in this case (Fig. 7). The laboratory data were not unusual. The serum protein showed no striking change varying between a low of 5.85 Gm. per cent to 6.85 Gm. per cent. On the last day of his intravenous regimen it was 6.66 Gm. per cent, albumin 3.96 Gm. per cent.

**Case 8.**—Hosp. No. D-10336: A. T., Negro, male, age 47, was admitted, January 22, 1940, to Homer Phillips Hospital. He had had a right lower quadrant mass of two weeks' duration; this was diagnosed as an appendiceal abscess and conservative therapy instituted. Because of increasing symptoms of extension he was operated upon five days later and a large spreading appendiceal abscess opened and drained. For the first four



postoperative days his course was quite stormy and repeated injections of caffeine were administered. Severe abdominal distention developed, the pulse was rapid, respirations labored. On the fifth postoperative day, amino-acids were added to the intravenous glucose, which resulted in a startling improvement, which continued thereafter. There was but one reaction during the course of the amino-acid therapy, consisting of a severe chill, unaccompanied, however, by any rise in temperature. The laboratory data were not significant. The serum protein four days after operation was 5.7 Gm. per cent, albumin 3.6 Gm. per cent; eight days later it rose to 6.7 Gm. per cent; albumin 3.8 Gm. per cent. There was no change in the red cell count. The metabolic data are represented in Figure 8, and show the high urinary output of nitrogen indicative of extensive "toxic destruction of protein."

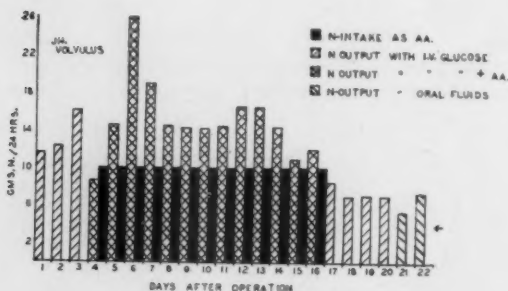


FIG. 7.

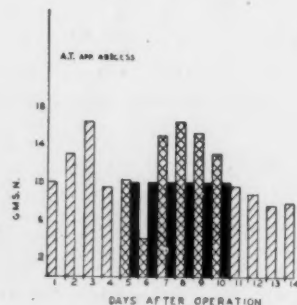


FIG. 8.

FIG. 7.—Case 7, and FIG. 8.—Case 8: The above charts represent two postoperative cases (see Case Reports). Note in both the large output of nitrogen in the urine (10 to 26 Gm. per day). The arrow in Figure 7 indicates what is about the normal output (5 Gm.). In both cases 4,000 cc. of 10 per cent glucose was administered each day; the amount of hydrolyzed casein was 80 Gm. (9.6 Gm. N.). Note that nitrogen balance was only occasionally achieved at this level of intake. (The low output in Case 8, on the sixth day, was due to loss of a specimen.)

There was no difficulty in achieving nitrogen balance in patients with low or moderate nitrogen excretion even when but 6.0 Gm. of nitrogen were injected per day (Figs. 1, 2, 3 and 4). As observed previously,<sup>3</sup> most fasting patients excrete about 4 to 5 Gm. of nitrogen a day when sufficient glucose is injected to meet caloric needs. Many of the cases described herein, however, showed a large output of urinary nitrogen, particularly following operations, amounting to as much as 26 Gm. per day; in these a positive nitrogen balance was, therefore, not achieved with regularity at the maximum intake of 9.6 Gm. of nitrogen per day (Figs. 5, 6, 7 and 8). Doubtless, with larger injections this could have been achieved. Nevertheless, favorable clinical effects were observed in several of these postoperative patients as soon as amino-acids were added to the intravenous glucose. This was particularly true in Cases 5, 6 and 8, which exhibited the largest output of nitrogen (see Case Reports).

In Cases 4 and 5, and less so in Case 8, definite evidence of serum protein regeneration was observed during the period of treatment. These observations are not decisive because the hypoproteinemia was not particularly severe. Indeed, few of the patients in the present series exhibited this defect to a significant degree.

COMMENT.—From the findings reported herein, the inference seems justified that a mixture of amino-acids prepared by the enzymatic hydrolysis



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of casein, when injected intravenously, is retained and, presumably, utilized by the body, sometimes even in a demonstrable increase in serum protein. Although few of the patients studied showed significant hypoproteinemia, of those that did two, possibly three, exhibited definite increases in serum protein and albumin while under treatment (Cases 4, 5 and 8). In other patients the therapy may have prevented a fall in serum protein; such a fall is a not infrequent experience in severely sick patients after operation. No such fall occurred in any of the patients receiving amino-acids. Although the present observations permit no dogmatic inferences as to the effect of intravenous amino-acids on serum protein regeneration, the achievement of positive nitrogen balance as well as the clinical improvement noted in many instances points to the beneficial therapeutic results of nitrogenous nourishment administered intravenously in this way. On the other side of the ledger are the difficulties encountered, the most serious being the occasional reactions observed. These reactions, I believe, are not an inevitable part of the procedure but are due to factors which may even now have been overcome by newer methods of preparation and administration of the enzymatic hydrolysate. With the achievement of a constantly uniform product, the use of amino-acids as a method of parenteral replacement of protein will undoubtedly have widespread application. While this use may not solve the fundamental problem of serum protein regeneration, I believe that, with all other protein needs met with amino-acids, a relatively small amount of blood, when necessary, will permit restoration of serum protein which can then be maintained for a sufficient length of time to permit normal relations to become established. The purpose of most parenteral alimentation, in surgery at least, is to clear temporary hurdles; by bringing patients into a more normal preoperative nutritional state, by breaking into a vicious circle induced by nutritional edema, and by permitting temporary gastro-intestinal rest, intravenous alimentation finds its most clear-cut indications. In this field the addition of nitrogenous nourishment should fill a long felt want.

An incidental finding in the present study concerns the tremendous output of urinary nitrogen in many patients during the postoperative period (Figs. 5, 6, 7 and 8). It is of considerable interest and importance to note the magnitude of this loss; thus in Case 7, on the fourth day, 26 Gm. of nitrogen were excreted, which is equivalent to the loss of almost two pounds of muscle tissue a day. These losses were due to the disease itself and occurred in spite of the fact that each day 1,600 calories, as glucose, were injected, thus sparing protein as far as their use for caloric needs are concerned. Evidence of such "toxic destruction of protein" has been observed in a severe burn by Lucido,<sup>9</sup> in postoperative patients, by Touw,<sup>10</sup> and in patients following extensive trauma, by Cuthbertson.<sup>11</sup> Its significance in the production of symptoms is suggested by the beneficial effects observed in several patients after much of the nitrogen loss was met by the addition of amino-acids to the intravenous glucose. These findings would seem to add a definite indication for such treatment in the postoperative care of very sick patients.

## SUMMARY

(1) In 35 adults a solution containing glucose, amino-acids and electrolyte was injected intravenously as the *sole* source of alimentation, with the particular purpose of parenteral protein replacement. The amino-acids consisted of a mixture obtained by the enzymatic hydrolysis of casein. The maximum amount of nitrogen administered was 9.6 Gm. per day, the calories, 1,600.

(2) Evidence of utilization was shown by: (a) The achievement of nitrogen balance; (b) increases in serum protein concentration; and (c) clinical improvement, particularly after serious operations.

(3) Large amounts of urinary nitrogen were excreted by many patients after serious operations, indicative of "toxic destruction of protein." The clinical improvement during treatment seemed to be associated with the partial or complete replacement of this loss of nitrogen by the intravenously administered amino-acids.

(4) Certain difficulties in the intravenous injection of the amino-acid mixture are described and discussed. These are being rapidly solved by newer methods of preparation of the amino-acid mixture and of the solutions made therewith.\*

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\* At the present time a 10% glucose 2½% amino-acid solution is prepared in the cold, immediately passed through a large capacity Berkefeld filter to remove pyrogens and autoclaved at once in 1000 cc. flasks for 30 minutes at 5 lbs. pressure. Thus far no febrile reactions have been observed with solutions prepared according to this much more simple method.

## THE RELATION OF PROPER PREPARATION OF SOLUTIONS FOR INTRAVENOUS THERAPY TO FEBRILE REACTIONS\*

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WIDESPREAD DEMAND for an inexpensive source of safe parenteral fluids has resulted from the recognition of the importance of maintaining a positive water balance as an adjuvant in hastening convalescence. Many hospitals prepare their own solutions in an endeavor to make adequate parenteral therapy economically feasible for all their patients. Other hospitals would like to reduce the cost of providing such solutions, but are loath to undertake the preparation of parenteral solutions because they fear the occurrence of untoward allergic or febrile reactions.

During the period between 1933 and 1936, a technic was developed at the Peter Bent Brigham Hospital which enables hospitals to prepare parenteral fluids safely and inexpensively. Since then, 250 hospitals have had experience with this technic. As a result, the technic and apparatus have become sufficiently standardized to warrant demonstration before this society.

There are but two requisites for a safe supply of parenteral fluid: A source of pure raw materials; and centralized responsibility for cleanliness in preparation of the solutions and apparatus. Any hospital in which major surgery is performed has the necessary sterilizing equipment and the trained personnel to whom such responsibility can be delegated safely.

Clinicians persist in adhering to numerous conjectures regarding the cause of intravenous reactions despite convincing laboratory and clinical evidence explaining the etiology of such reactions. In 1911, it was shown that chemically pure distilled water would not cause reactions when injected intravenously;<sup>20</sup> that such water was readily contaminated and made pyrogenic by air-borne bacteria;<sup>6</sup> and that Berkefeld filtration did not remove the offending substance.<sup>4</sup>

More recently (1923), such pyrogens were demonstrated to be filterable, thermostable exotoxins removable by distillation in a still designed to prevent entrainment. If kept sterile, pyrogen-free water remained so.<sup>11, 12, 13, 14, 15</sup>

Subsequently, it was found that pyrogenic water could be rendered innocuous by heating it to 284° F. (38 p.s.i. gauge) for 30 minutes.<sup>1</sup> Adsorptive filtration was also found to be effective in removing the objectionable proteins.<sup>2</sup>

The application of these factors resulted in the rapid development of commercial sources of reliable parenteral fluids and in numerous demonstrations that hospital-made solutions are safe, economical, and practical.<sup>5, 7, 8, 9</sup> Ac-

\* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

cordingly, rational parenteral therapy should be available in modern hospitals; and the volume, velocity, temperature, and composition of the injection may be left entirely to the discretion of the clinician. The intravenous injection of chemically pure, sterile solutions will not cause untoward reactions.

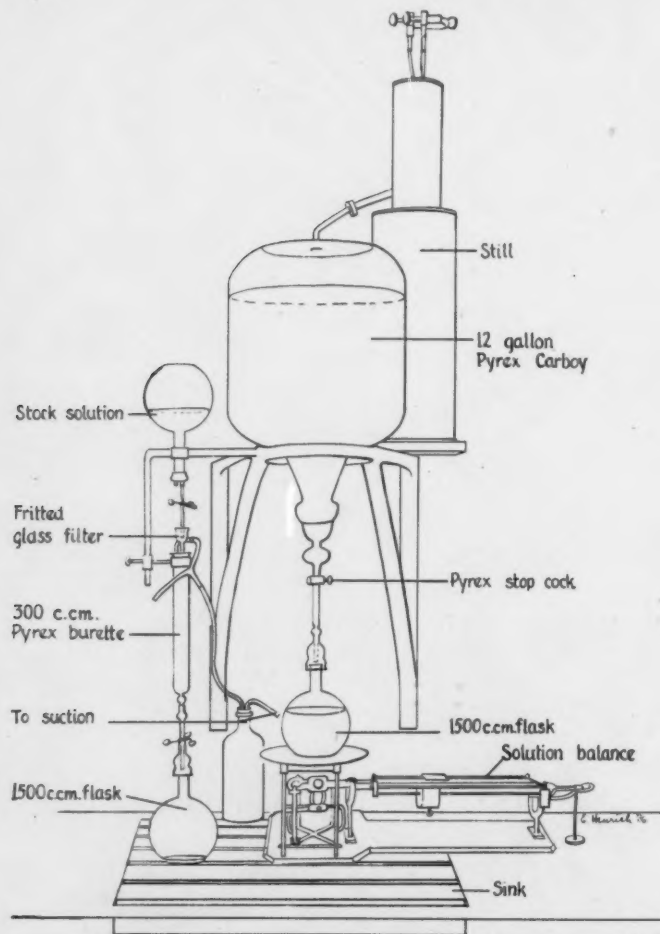


FIG. 1.—Arrangement of apparatus to facilitate the preparation of parenteral solutions. Distilled water, for immediate use only, is collected in an inverted pyrex carboy. The solutions are made by diluting a filtered concentrate gravimetrically.

*Distilled Water.*—Singly distilled water is sufficiently pure for intravenous use provided several precautions are taken to prevent pollution of the distillate. First, intelligent operation and maintenance of the still are essential.

Second, chemically pure distilled water cannot be stored unless it is hermetically sealed in sterile containers; hence, distilled water must be collected in a storage tank just large enough to contain a working supply. An inverted pyrex carboy (Fig. 1) fitted with a glass stopcock is best because such a container can be drained dry and has no gauge glasses, faucets, or valleys where

## PREPARATION OF PARENTERAL FLUIDS

residual water may pool and support bacterial growth which pollutes subsequent collections of distillate. Such carboys should be drained as soon as there is no immediate use for distilled water.

Third, the purity of the water must be determined frequently. Since pure water is a comparatively poor conductor of electricity, its specific conductance is an excellent measure of its purity. The distillate from a well-designed, properly operated still should have a maximum conductivity\* of  $2 \times 10^{-6}$  mhos at  $20^{\circ}$  C. One part per million of chloride ion will increase the conductivity of distilled water about 50 per cent. The presence of electrolytes in freshly distilled water indicates contamination with tap water either by entrainment or by leakage from a faulty condenser. Then it may be assumed that the water has also been contaminated by pyrogenic substances which accompanied the electrolytes. Therefore, the efficiency of a still can be checked quickly and accurately by determining the specific resistance of the distillate by means of a 1,000 cycle Wheatstone bridge. Some stills produce impure water sporadically and should be equipped so that the purity of the distillate is checked continuously.

Biologic methods must be employed to identify actual pyrogen content. The most readily applicable test is that of injecting 10 cc. of the questionable solution into the ear vein of a rabbit and determining the rectal temperature at hourly intervals for three or four hours. The rabbit's normal temperature ranges from  $101.2^{\circ}$  to  $103^{\circ}$  F. under standardized conditions. The febrile reaction which results from the injection of pyrogen raises this to  $105^{\circ}$ – $107^{\circ}$ .<sup>11, 14</sup>

*Chemicals.*—Although the United States Pharmacopeia does not specify dextrose suitable for intravenous use, U.S.P. XI or C.P. anhydrous grades of chemicals are usually satisfactory. Sodium chloride and dextrose are purchased most economically in drums of 25 and 200 pounds respectively. Careless transference of the chemicals must be avoided and any which touches the hands or drops upon the balance or table top should be discarded rather than be returned to the bulk container.

There is an advantage other than economy in buying the chemicals in bulk because, once the purity of any lot has been established, a supply of known quality is available. Dextrose may contain protein split products, and/or various acid dehydration products of dextrose formed by side reactions during the manufacture of dextrose.

The protein contaminant is present in the form of amino-acid-carbohydrate condensations or polypeptide intracrystalline occlusions. These compounds undergo heat denaturization during sterilization and form white, flocculent precipitates in the final solutions. They can be detected by denaturing them

\* Conductance, the reciprocal of resistance, is measured by the ratio of the current flowing through a conductor to the difference of potential between its ends. The practical unit of conductance, the mho, is the conductance of a body through which one ampere of current flows when the potential difference is one volt. Conductivity is measured by the quantity of electricity transferred across unit area per unit gradient.



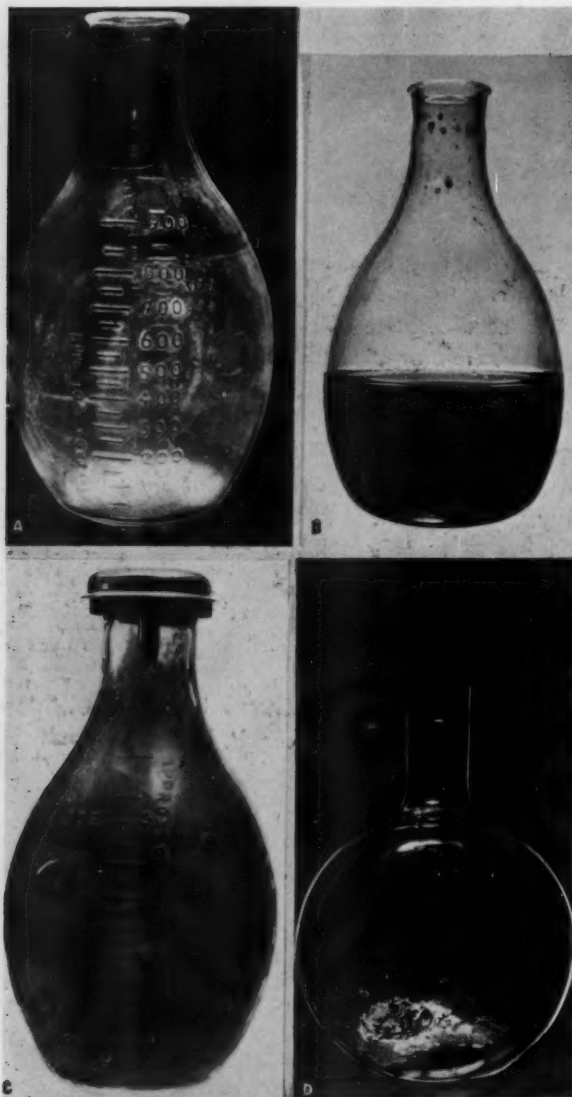


FIG. 2.—(A) Clean glassware is free of this white, opalescent film of insoluble alkaline earth soaps formed by the interaction of soap and/or detergents and the calcium or magnesium salts which are found in tap water or soil. A film of distilled water remains spread over the surface of clean glass as the water is poured off. Grease or other soil causes this film to "break" into the numerous droplets illustrated (B). Bacterial growth in residual blood (C) or solution (D) left in apparatus may produce pyrogen. Unless thoroughly cleaned, such apparatus may contaminate pure solution with pyrogen.

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mechanically by passing 50 per cent dextrose through the clarifying bowl of a Sharples centrifuge or forcing it through an atomizing jet. In either case the impure solution becomes opalescent and dirty white or yellow curds separate out on standing. Such polypeptides can be removed by adsorptive filtration or ultrafiltration.

The dehydration products are chiefly hydroxymethyl furfural and levulinic acid.<sup>21</sup> The former is colorless, but, on aging, it degrades to levulinic acid, a dark brown compound. This conversion occurs rapidly in hot aqueous solutions and accounts for the yellow color (often mistaken for caramelization)

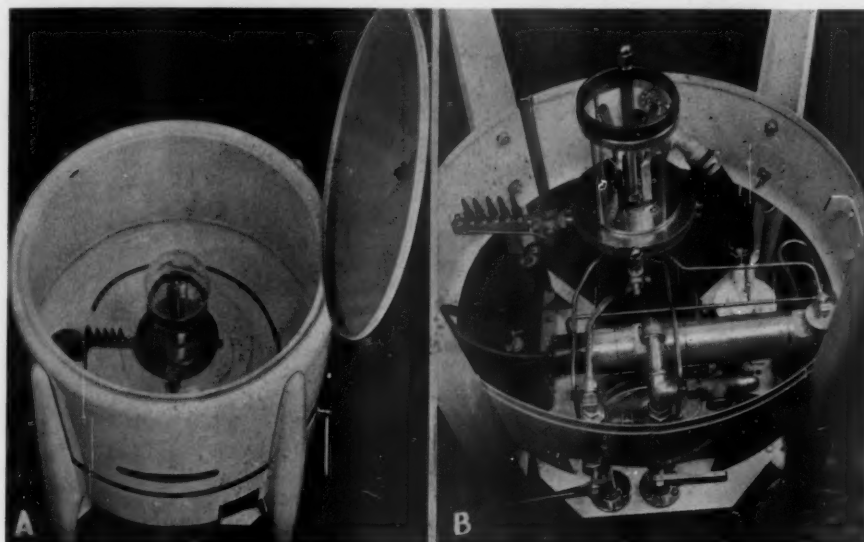


FIG. 3.—A mechanical washer (A) most readily cleans the inner surface of glassware, tubing, and needles by scouring them with hot detergent solution. The washer uses the detergent solution repeatedly, automatically filtering, reheating, and pumping it through suitable jets under high pressure. The flask washer is shown at the upper center (B); the needle and tubing nipples can be seen at the left.

developed during sterilization of some dextrose solutions.

The acceptance of any particular lot of chemical also depends upon the quantity of particulate matter contaminating it. Excessive dust not only clogs the filters quickly, but is evidence of careless handling prior to packaging. The finding of a shoelace tip or a dried insect indicates contamination of a degree likely to introduce foreign proteins into the chemicals. Dirty chemicals must be rejected.

**Glassware.**—Pyrex glassware is the most satisfactory, not only because of its high resistance to mechanical and thermal shock, but because its stable annealed surface resists hydrolysis by the solutions. The alkaline film formed at the glass-liquid interface of a soft glass flask may cause polymerization of the dextrose during sterilization.

To be chemically clean, glassware must be freed of the initial soil as well as of insoluble deposits (Fig. 2 A) resulting from the interaction of washing agents (soaps and detergents) and water or soil containing more than traces

of alkaline earths<sup>3, 10</sup> (Ca. and Mg.). Clean glass should show no "water breaks" (Fig. 2 B) in the film of distilled water left after the final rinsing, and it should be crystal clear when dry.



FIG. 4.—The containers are rinsed by inverting them over a spray of freshly distilled water. The stainless-steel sprayer illustrated conserves distilled water by shutting it off when not in use and also by metering the amount used. When the flask is first inverted over the spray, the cup at the bottom is empty. The rinse water collects in this cup, giving an idea of the amount used as well as rinsing the outside of the neck. One hundred cubic centimeters of distilled water (enough to fill the cup twice) suffices to remove all the alkali.

Dried blood (Fig. 2 C) and closely adherent bacterial growths (Fig. 2 D) are the usual types of soil encountered. Dried fungi are particularly difficult to remove. They may be invisible until hydrolized during sterilization, at which time they swell and become opaque and may be mistaken for wisps of cotton floating in the solution. Because glassware is often used in the

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laboratory or utility room, residues of feces, urine, pus, and transudates are often encountered. The most tenacious soil is a greasy film which accumulates when the glassware is used repeatedly without adequate cleansing.

The containers are most readily cleansed in a mechanical washer (Fig. 3) which forces hot detergent solution\* through jets under sufficient pressure to scour the inner surface. This mechanical action augments the effectiveness of a good detergent and cleanses in 15 or 20 seconds. The glassware is rinsed thoroughly with freshly distilled water by inverting it over a jet (Fig. 4) which sprays distilled water on the entire inner surface. Usually 100 cc. of water suffice to rinse away all the alkali. The container is then inverted to drain.

The stainless-steel stoppers and rubber bushings are cleaned by scrubbing them thoroughly with hot detergent solution and rinsing them in freshly distilled water.

*Filters.*—Fritted glass or porcelain filters are readily cleaned by immersing them in a hot solution (175° F.) containing ½ per cent each of sodium nitrite and sodium chlorate in concentrated sulphuric acid. The acid is rinsed from the porous disk by running distilled water through the filter in the reverse direction until the rinsings are neutral to litmus paper or until the conductivity of the rinsings approaches that of the original distilled water.

*Equipment.*—The equipment chosen for the preparation of parenteral fluids should provide for easy sterilization, safe storage under hermetic seal, and ready administration from the original container.<sup>16, 17, 18, 19</sup> Such apparatus (Fig. 5) consists of a container which can be hermetically sealed by means of a rubber bushing and stainless-steel stopper. The elements of the seal are assembled prior to sterilization so that possible contamination during sealing is avoided. The contents of the flask can be infused by substituting a special "vent tube" through which the fluid leaves the inverted container by gravity, for the stainless-steel stopper.

*Container.*—The graduated container is mold-blown of thick Pyrex glass in a shape designed to withstand the water-hammer which results when fluids under high vacuum are jarred. Its wide mouth and short neck facilitate cleaning. The contour of the mouth and lip is such that the rubber bushing is held securely in place.

The rubber bushing is molded of nontoxic, heat-resistant rubber which retains its resiliency after repeated sterilization and does not become tacky and stick to either the container or the stopper. It is shaped to cling firmly to the mouth of the container. The frustum of the bushing fits snugly against the inwardly tapering portion of the neck of the container to prevent the bushing from being pushed inward during sealing, or from being drawn into the flask as the vacuum is formed. The elastic periphery of the skirt clings to the lip of the flask, holding the bushing in position when the stopper is withdrawn or when the container is inverted in the dispensing position.

\* Any commercial dishwashing compound which leaves the glass crystal clear on drying is satisfactory.

The stopper is fabricated of a corrosion-resisting, stainless-steel to withstand the attack of saline solutions, as well as to resist tarnish from an atmosphere of air or steam. The mushroom-shaped stopper is essentially a rugged cap, which covers and protects the rubber bushing, and a stem which actually provides the closure. A longitudinal channel cut into the lower third of the stem provides an adequate vent for the escape of air and steam during

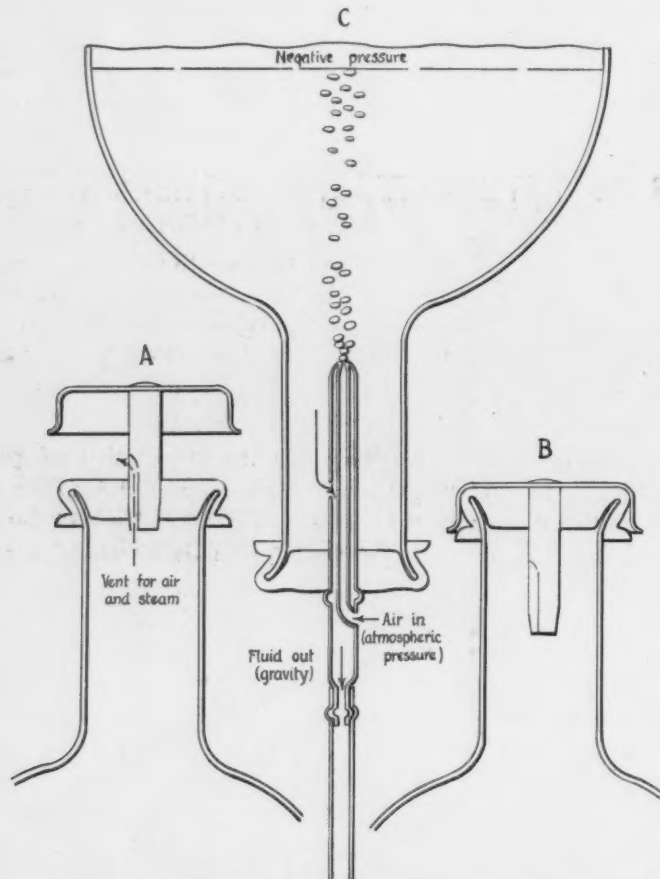


FIG. 5.—Easy preparation, sterilization, safe storage, and ready administration are provided in this simple container. (A) The channel in the steel stopper provides for the escape of air and steam during sterilization. (B) A vacuum seal is produced by inserting the stopper into the bushing and permitting the flask to cool. (C) Air enters the capillary orifice in the vent tube to relieve negative pressure within the inverted flask.

sterilization (Fig. 5 A). A rush of steam through this channel, due to the sudden ebullition of vapor following faulty venting of a sterilizer, serves to warn the alert operator that the solutions have been spoiled. On removal from the sterilizer, the stopper is rocked into the bushing so that the solid portion of the stem forms a hermetic seal with the bushing (Fig. 5 B). Precipitation of the water vapor and contraction of the fluid during cooling produces a high degree of vacuum (29 inches Hg.) which aids in maintaining



the seal. The water-hammer click which is obtained by jarring a sealed flask gives evidence that the container has been properly sterilized and sealed.

The fluid is dispensed from the original container by substituting the hard glass vent tube for the steel stopper (Fig. 5 C). This tube comprises a pair of concentric glass tubes, the external diameter of which corresponds to the aperture in the bushing, so that it makes a water-tight fit with the latter. Two circumferential ribs or beads serve to position the tube firmly in relation to the bushing. Fluid enters the annulus of the vent tube through a small orifice just above the inner bead and leaves through the tubing nipple at the outer end of the vent tube, permitting free gravity flow from the inverted flask.

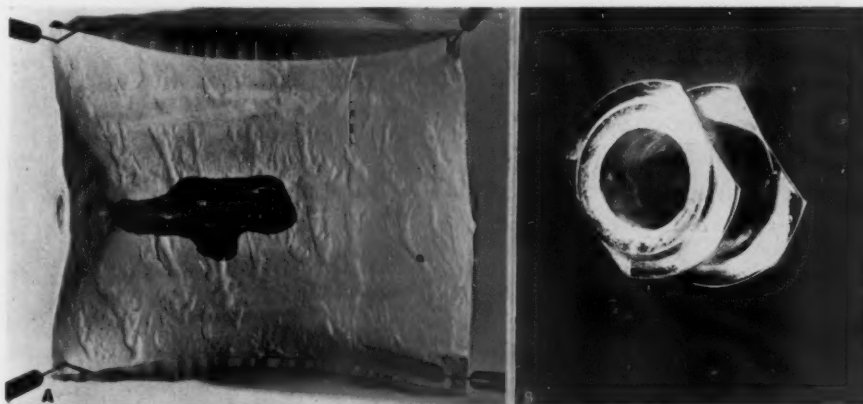


FIG. 6.—Pits, wrinkles, and mold marks on the inner surface of rubber tubing catch blood or hold residual solution where bacteria may grow. Tubing with a smooth inner surface can be cleaned readily, whereas the bits of the dried blood clot (A) or colonies of bacteria lodge tenaciously in the hollows of the rough surface. Bacterial growth in the lumen of the cannula or hub of a needle may contribute pyrogen. Even cursory inspection of the hub should have detected the clot illustrated (B). The cannulae must be reamed with a tightly fitting stilet to insure cleanliness.

Air is metered into the flask to overcome the increasing negative pressure caused by the escape of fluid. This is done by means of the inner tube which communicates with the atmosphere just below the outer bead and leads inwardly to a capillary orifice at the upper end of the vent tube. This capillary is small enough to prevent the fluid leaking through the air vent when the negative pressure is too low to support the static head of the fluid in the flask.

*Rubber Tubing.*—In selecting rubber tubing for use in parenteral therapy, it is essential that the inner surface be free from pits, wrinkles, and mold marks, where blood and bacterial residues lodge and make cleaning difficult (Fig. 6). The surface of rubber exposed to the fluid can be decreased markedly by selecting a tubing of small inside diameter ( $\frac{1}{8}$  inch). A small lumen also facilitates the expulsion of air from the system, since fluid tends to run through it as a solid column rather than to trickle down one side as in a gutter. Any nontoxic rubber can be used, but it is more economical to select a rubber compounded to insure maximum heat resistance. Tubing available at present will withstand 75 sterilizations before it loses its elasticity.

*Preparation of Solutions.*—The avoidance of mass filtration and bulk dilution of solutions will be found convenient in most hospitals. The problems entailed in handling large quantities of fluid can be avoided by a technic which also limits potential spoilage due to improper mixing, faulty filtration, careless contamination or uncleanness, to individual flasks. Such technic is based upon the filtration of a relatively small proportion of the final solution in the form of a concentrate. This concentrate is then diluted with distilled water which should contain no particulate matter if properly distilled and collected. In the average hospital, the concentrate is filtered most advantageously into a large volumetric burette whence a suitable portion is measured into a container and distilled water added until the proper dilution by weight is made (Fig. 1).

Five per cent dextrose solution is prepared from a fresh stock solution made by adding hot distilled water to 1,000 Gm. of chemically pure dextrose, previously weighed out in a counterbalanced flask, until a net weight of 2,355 Gm. has been reached. The flask is stoppered with a clean rubber stopper and shaken until solution is complete. This stock solution is then filtered through a fritted glass (17 G 5/3), porcelain filter (F.G.-450-10), or adsorptive filter (Seitz uhlenhuth 60 Mm. germicide EK), with the aid of suction, directly into a pyrex burette. The filtrate should be crystal clear and colorless. The stock solution can be decolorized and clarified if necessary by adding 1 to 2 per cent activated charcoal (Norit\*) prior to filtration. One hundred cubic centimeters of the filtrate are measured into a counterbalanced, pyrex container, and distilled water is added to a net weight of 1,066 Gm. A clean rubber bushing is fitted into the mouth of the flask, its skirt is turned down, and the channeled stem of the steel stopper is partially inserted into the bushing. The solutions are sterilized immediately in an autoclave at 250° F. (exhaust line temperature<sup>18</sup>) for 30 minutes. After sterilization the steam supply to the autoclave is shut off to permit the autoclave to cool to 200° F. before it is opened. In this way, concentration of solution resulting from the ebullition of steam following sudden relief of pressure is avoided. As the flasks are removed from the autoclave, the steel stoppers are pushed in to complete the seal. The sterile, sealed solutions can be stored indefinitely without impairing their value as safe parenteral fluids.

*Preparation of Intravenous Kits.*—The establishment of a source of chemically pure parenteral fluids is futile unless an equally safe supply of apparatus for its administration is constantly available. Bacterial growth in residual solution or blood in such equipment produces pyrogen which must be removed by adequate cleansing with pyrogen-free water. Chemical cleanliness of the inner wall of the vent tubes, rubber tubing, observation tubes, and needles is essential for safe, reactionless infusions.

The cleansing of such apparatus must be done immediately before sterili-

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\* Norit (decolorizing carbon—P1731), Research Laboratory, Eastman Kodak, Rochester, New York.

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zation, because bacteria are likely to grow in the moisture left in the apparatus to insure sterilization.

The rubber tubing is cleaned by slipping one end over the nipple of the automatic washer (Fig. 3) and flushing the lumen for one minute with detergent solution under pressure. Freshly distilled water is then run through the tubing for ten seconds to remove the detergent and leave the inner surface chemically clean. No attempt is made to dry the lumen of the tubing.

The small glass parts, vent tubes and observation tubes, can be cleaned rapidly by sucking hot detergent solution through them. This can be done

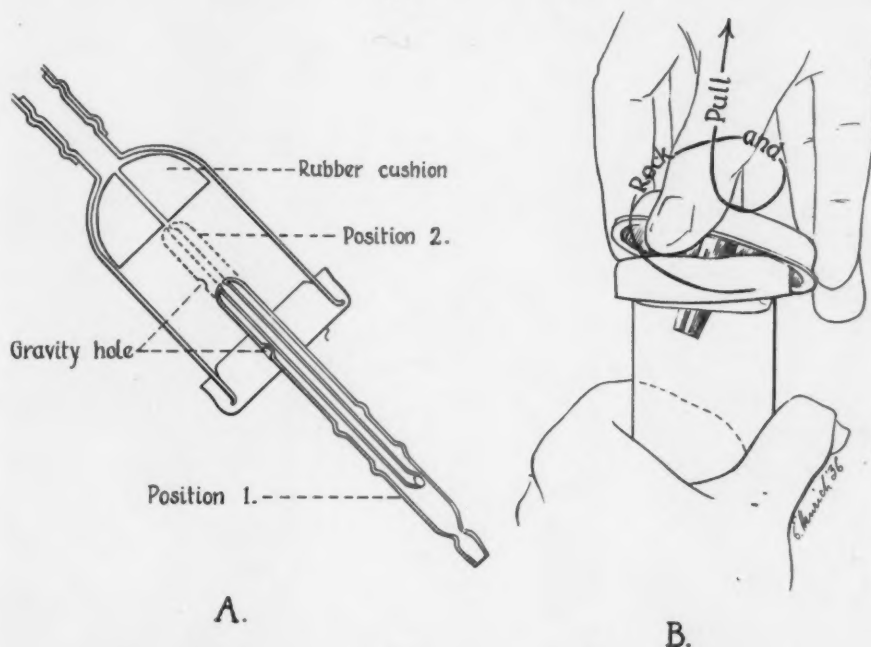


FIG. 7.—The pyrex vent tubes are easily cleaned by sucking hot detergent solution through them (A). In position 1, the gravity outlet is occluded while the air tube is rinsed; at 2, both passages are cleansed.

The stainless-steel stopper is readily removed by a rocking, spiral motion (B).

most easily in the case of the pyrex vent tubes by using a special holder which permits positioning of the tube, so that the capillary vent and the fluid passage can be cleansed and rinsed separately (Fig. 7 A).

Needles are cleaned by locking them on the Luer-lock needle adapters provided for the purpose in the mechanical washer and forcing hot detergent solution through them. They are rinsed with distilled water and inspected critically, not only for sharpness, but also for weakness which might cause unexpected breakage. This is done by holding the hub firmly while the tip is sprung through an arc. Those which have been weakened will snap off or bend at the junction of the hub and needle. Needles should not be sterilized with stilet in place because the electrolytic action set up between the stilet and the needle causes early corrosion and weakening.

The various elements of the infusion apparatus are reassembled without drying, and the equipment is arranged in a clean aluminum tray (Fig. 8A). This tray is inserted into the sterilizing envelope, the inner flap of which is tucked beneath the pan and the outer flap securely pinned. The kits must be sterilized without delay. The residual water inside the rubber tubing is vaporized in the sterilizer and provides the moisture essential for sterilization. It is important to have the tubing moist because it is difficult to clear sufficient air from a length of dry coiled rubber to attain sterilizing conditions.

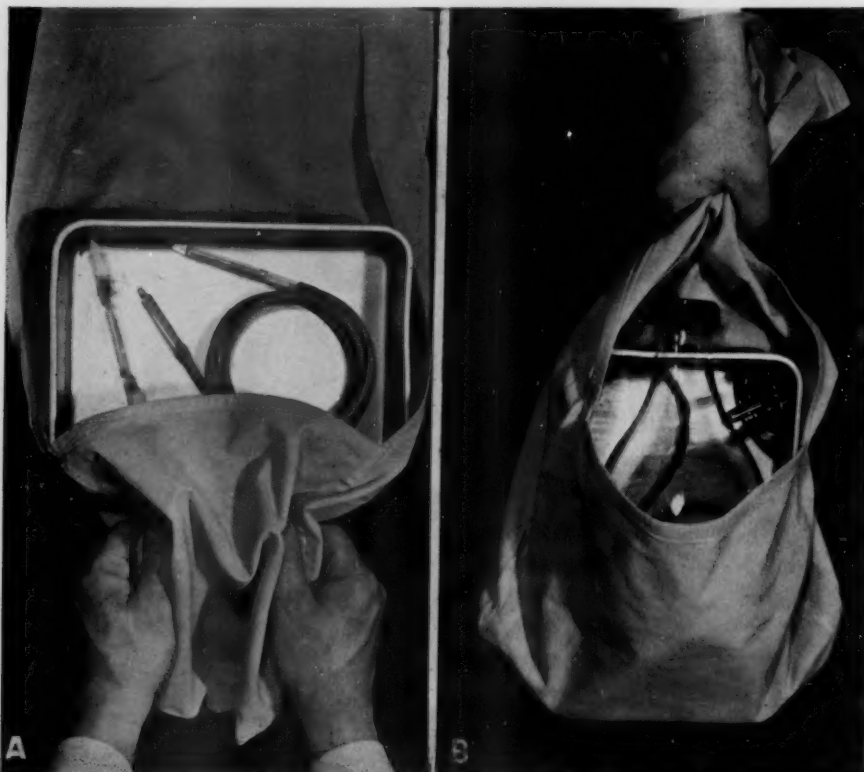


FIG. 8.—The arrangement of the elements of the infusion apparatus assembled in the sterilizing tray is illustrated (A). The tubing is coiled so that the vent tube is uppermost. The tray is easily extruded from the sterilizing envelope by forcing the sides of the envelope together. The envelope also serves as a convenient means of returning the apparatus to the supply room (B). The vent tube is removed from the bushing and put into the tray along with the needles and steel stopper. The bushing is left in place to prevent accidental chipping of the lip of the container.

*Sterilization of Kits.*—The kits are packed into a dressing sterilizer so that the bottoms of the aluminum trays are in a vertical position. This permits the steam to displace the air and results in the rapid development of sterilizing temperatures. It is advantageous to sterilize them alone or with loosely wrapped rubber goods because little heat is required to bring the kits to sterilizing temperature. They should be sterilized for 30 minutes at 250° F. (exhaust line temperature).

After sterilization the envelopes are dried by leaving the sterilizer door

ajar for 15 minutes while the steam pressure is maintained in the jacket. If the kits are stored with the trays inverted, there is little danger of contamination from dust and they can be kept until needed.

*Administration.*—When an infusion is ordered, it is necessary to obtain only an intravenous kit and a container of the appropriate solution. The sterility of the solution is tested by striking the inverted flask sharply with the palm, driving it suddenly away from its liquid contents. The liquid subsequently strikes the flask again producing a metallic water-hammer click. This phenomenon indicates a vacuum of 29 inches of mercury—assurance that the flask was heated sufficiently to drive off the air prior to sealing, and that the hermetic seal has been maintained. The fluid is administered from the original container by removing the steel stopper by a spiral, rocking, twisting motion (Fig. 7 B). An inrush of air, as this is done, is additional evidence that the flask has not been opened following sterilization.

The outer flap of the sterilizing envelope is loosened and the corners of the envelope are grasped and pushed together to extrude the aluminium tray from the envelope (Fig. 8 A). This provides, simultaneously, a sterile field and a receptacle to catch the liquid when the air is being expelled from the rubber tubing.

The portion of rubber tubing stretched over the nipple of the pyrex vent tube is then grasped and the latter is "wiggled" into the hole in the rubber bushing until the groove between the shoulders of the vent tube is seated in the rubber bushing (Fig. 5 A). This tube acts as a valve for the admission of air to overcome the negative pressure created in the container as the fluid leaves under the influence of gravity. Since the surface tension across the capillary orifice at the top of the valve is sufficiently great to support the column of water in the container, there should be no leakage of solution from the air vent once a negative pressure has been established in the flask. This is done conveniently by inverting the flask, hanging it in the split-ring bracket, and permitting the solution to run through the rubber tubing into the aluminium pan before the needle is attached.

The needle is readily withdrawn from the hour-glass sterilizing tube by removing the cotton plug and inserting the ground-glass tip of the observation tube into the hub of the needle. The needle can be attached firmly enough to prevent dropping or contaminating it.

The rate of injection can be predetermined (within limits) by holding the needle level with the vein into which it is to be inserted and varying the pressure head by raising or lowering the flask. For all practical purposes either a 19 or 21 gauge needle will provide an ample range of flow. The infusion is now ready to start.

More fluid than is contained in one flask may be given by substituting a second flask as the first one is emptied. This is done by clamping off the rubber tube with a Hoffman clamp before removing the vent tube from the first flask. The vent tube is then inserted into the bushing of a fresh flask of solution, the container inverted, and the Hoffman clamp removed.



After the infusion has been completed, a small gauze sponge is held gently over the skin puncture and the needle is withdrawn. Pressure is maintained over the sponge for at least five minutes until the hole in the vein has sealed off. This precaution prevents extravasation of blood into the subcutaneous tissues with the subsequent unsightly discoloration of the overlying skin.

*Return of Apparatus to the Central Supply Room.*—The infusion apparatus is removed from the split-ring bracket and placed in the aluminum pan, without being disassembled, along with the stainless-steel stopper, extra needles, and the hour-glass sterilizing tube. The pan is then inserted longitudinally into the sterilizing envelope (Fig. 8 B) and returned to the central solution room. The long flap of the envelope serves as a handle so that five or six sets can be carried conveniently in one hand without danger of loss or breakage.

Thus, the preparation of safe parenteral solutions depends upon a clear understanding of the meaning of the term "chemically pure" and its differentiation from the word "sterile." The technic, here outlined, enables any hospital to prepare parenteral solutions at a cost which permits adequate therapy to be given all patients in whom it is indicated.

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*Discussion.*—DR. DALLAS B. PHEMISTER (Chicago, Ill.): Fluid and electrolyte need from local loss of plasma was discussed in connection with burns. While this is the most important cause of local plasma loss calling for the therapy outlined, it is not the only one. Injury to a large part of the body may do it, but operations rarely are sufficiently extensive and traumatizing to cause local plasma accumulation or escape which calls for replacement therapy. In the following case of common iliac vein thrombosis there was rapid loss of plasma into the limb which was sufficient to produce the circulatory failure. A woman who was hospitalized with a generalized moniliasis of the skin, a suppurative otitis media, and an unrecognized carcinoma of the pancreas, developed, over night, a rapidly increasing swelling with mottling of the skin of the left lower limb. When seen late in the forenoon she showed marked evidences of shock and no pulse was palpable in the markedly swollen and discolored extremity. Her condition grew worse and she died at 7 P.M., before which, however, the right limb also began to show slightly similar changes.

At autopsy, there was found, aside from the above mentioned changes, a fresh thrombophlebitis completely blocking the left common iliac vein and partly blocking the inferior vena cava. From measurements of the lower limbs, it was calculated that the volume of the left one was about four liters greater than that of the right. There were no changes found to explain the immediate cause of death except the great loss of plasma into the limb.

Most of the emphasis in the discussions was placed on the water, plasma and electrolyte needs of the patient and less on the accompanying erythrocyte needs which, obviously, may be difficult to separate.

It should be borne in mind that in cases of marked postoperative circulatory failure, blood transfusion may be more efficient than fluid and electrolyte administration even though there has been no appreciable loss of blood at operation. Also, this statement may sound like heresy but in sick patients who are to have extensive operations, it may, under circumstances, be advisable to operate more rapidly than usual, with greater blood loss and greater trauma to tissues in order to save the patient from prolonged general anesthesia. The blood loss should be compensated for by blood transfusion (given simultaneously). One should balance all of the factors that come into play in an operation and utilize the ones that are least harmful, and time saved at the expense of some blood loss, if it is adequately treated by blood transfusion, may be of greater importance than meticulous hemostasis and a more prolonged operation.

DR. DAMON B. PFEIFFER (Philadelphia, Pa.): In considering what to say in the discussion of this symposium, with its breadth, width, and depth, I feel very much like Doctor Walter did this morning: It is quite impossible even to touch upon all the various points of interest, and it seems to me better, therefore, to try to add one little point which has occurred to us in the Abington

Memorial Hospital as a result of our attempt to apply these plans and principles.

Pardon me just a moment of reminiscence. At the next to the last Philadelphia meeting, which I think was 13 years ago, I read a paper on "Alkalosis Simulating a Case of Nephritic Uremia." That was just after Van Slyke had done his fundamental work on the  $p_H$  of the body fluids, pointing out the normal zones with the compensated zones on each side and the uncompensated zones and dangers. Acidosis was very much in the public eye, and the term "alkalosis" was just coming into use. Haden and Orr, Gamble and others had written very illuminatingly on the subject and explained certain deaths after upper abdominal operations as a result of dislocation of plasma structure. The pediatricians were quite alive to these humoral conditions as a result of the susceptibility of children to such abnormalities, but the subject was, by and large, not at all diffused, certainly not to me, for I happened to have heard just enough of it to enable me to solve this one case.

The patient was a man who had had a long history of duodenal ulcer followed by a cicatricial stenosis and had formed the habit of vomiting. He could vomit almost at will and so pump out his stomach. He was brought into the hospital several times in a stuporous condition. His urine contained albumin, blood, and casts, and he was regarded and treated as a uremic. He was in deep coma and markedly dehydrated when I was asked to see him, not because I was expected to add anything as a surgeon but because I knew the family. In going over him, it struck me that it might be the new disease "alkalosis." His blood chemistry figures were as follows: Chlorides 200, plasma  $CO_2$  80; and blood urea nitrogen 112. I suggested that instead of withholding salt on account of the supposed nephritis he be given sodium chloride in large quantities until his plasma chloride level was up to normal. This was done. As his plasma chlorides rose, the blood urea gradually fell, and about 24 hours later he began to come out, and the next day he was only a little confused, and the following day he was completely himself mentally. In a week I was able to perform a jejunostomy and later on a gastro-enterostomy. He got entirely well.

The importance of this case, and the fact that we were dealing with a hitherto unrecognized condition, impressed profoundly not only me but also Dr. John Eiman, who is now at Abington Memorial Hospital. For several years, the question of water balance and acid-base equilibrium has been the major surgical problem of the Abington Memorial Hospital, to the extent that at times I fear we have made ourselves a little ridiculous. However, the problem as it has resolved itself to us is not so much any more in the understanding of the situation (although I am free to admit that we do not understand it at all, there is a great deal yet to be done) as in the difficulties we have in the correct application of these fundamental principles at the bedside.

We have developed rules which enable us to learn a great deal from the amount of urine. Dr. Walters, to-day, mentioned that as long as the urine output was 1,000 cc. or more, you could feel safe. That is true, by and large, but there occur a few cases in which the situation is much more complicated and which require a great deal of acumen and, certainly, a modicum of chemical knowledge to determine just what is going on and what your replacement must be and how much. Furthermore, there are certain difficulties in getting the data that are necessary, that is, the nurse, or the person who collects the specimens, must be absolutely accurate and must appreciate their importance. There must be somebody to supervise the nurse, to see that specimens are not thrown away. Then there is the question of recording. If you put them on the ordinary hour chart, it is a bit hard to dig them out and visualize what is

**ABINGTON MEMORIAL HOSPITAL, Abington, Pa.**

WATER AND SOLUTE CONTROL CHART

		Milliequivalents per Liter			
		110			
		100			
		90		NaCl	Normal
		80			
		70			
		60			
		50			
		40			
		30			
		20		HCO <sub>3</sub>	Normal
		10			
		0		Urea	Normal
cc.					
7300					
7000					
6500					
6000					
5500					
5000					
4500					
4000					
3500					
3000					
2500					
2000					
1500					
1000					
500					
0					
INTAKE					
OUTPUT					
Glucose					
M/6 Lact.					
Blood					
NaCl					
OUT: NaCl					
Urine Ketones					
Blood Pressure					
Hematocrit					
Plasma Proteins					
Colloid Pressure					
DATE					

Name	Age	Service of Dr.	Room Ward
Diagnosis		Interne	Form 75

Another matter was the education of the younger men, the resident surgeon and intern. While we were so keen on the matter and discussing it all the time and talking about it in our stag meetings, everybody was keenly alive, "salt and water conscious," but when we could no longer afford to dwell so



much upon this matter, the successive generations came along without adequate instruction in the fundamentals. We found that we could not turn these things over to our younger men, as we do so many details, and very properly,

## REVERSE OF WATER AND SOLUTE CONTROL CHART

**T**HE purpose of this chart is to enable the clinician to evaluate grossly at a glance the state of hydration and solute balance in a patient. The amount of water held in the body is chiefly determined by the quantities of certain solutes contained in the body fluids, mainly the chlorides, bicarbonate, urea and glucose. In normal concentrations, urea and glucose play only a minor role but become important factors when the amounts are markedly increased.

For practical purposes the effective concentration of solutes in the blood can be estimated by adding the plasma chlorides, bicarbonate and blood urea in terms of milliosmols. These fractions represent about 90% of all the crystalloids of plasma.

For more accurate studies all electrolytes, measured by the total base, the total NPN and glucose must be considered. This applies especially to cases in which the organic acids are markedly increased, as in starvation ketosis and in diabetes.

In the majority of normal cases the effective concentration of solutes in plasma, i.e., the sum of chlorides, bicarbonate and urea, varies from 215 to 240 milliosmols. Cases showing values of 20 or more mOsm below or above the normal zone must be regarded as requiring prompt and special attention. This applies particularly to patients with large amounts of organic acids and high blood sugar.

Normal distribution of fluids between the capillaries and interstitial tissue spaces depends on the normal amounts and integrity of plasma proteins, (Total 6-7.4 gms./100 cc., A.G. ratio 1.5-1.8, colloid osmotic pressure 345-385 mm. water). If patients are maintained on parenteral feedings for a week or more, special attention must be paid to the plasma proteins and deviations from the normal corrected by either whole blood or plasma transfusions. Unless protein faults are corrected, very little will be accomplished by the adjustment of the crystalloid imbalance.

If a patient depends mainly on parenteral intake, physiological saline should be substituted by Ringer's Solution after the third day. Further, in order to supply the vitamin requirements such a patient should be given intravenously at least 30 mgms. of Ascorbic Acid (in severe infections this should be increased to 60-100 mgms.) and 1 mg. Thiamin Chloride daily.

The upper part of this chart shows the concentration of plasma chlorides and bicarbonate in milliequivalents and the whole blood urea in millimols per liter. (Record the graphs as follows: Chlorides—green; Bicarbonate—blue; Urea—black.)

**NORMAL ZONES:** Plasma NaCl 560-600 mgms. % or 96-102 mEq/L  
Plasma CO<sub>3</sub> 45-65 vols. % or 19-26 mEq/L (bicarbonate)  
Blood Urea N. 7-15 mgms. % or 3-6 mEq/L

**CONVERSION VALUES:**

1.  $\frac{\text{Plasma NaCl in mgms. \%}}{5.85} = \text{chloride in mEq/L}$   
Chloride in mEq/L  $\times 1.86 = \text{mOsm}$
2.  $\frac{\text{Plasma CO}_3 \text{ vols. \%} \times 0.43}{\text{Bicarbonate in mEq/L} \times 1.86} = \text{mOsm}$
3.  $\frac{\text{Blood Urea N. mgms. \%}}{2.8} = \text{Urea in millimols} = \text{mOsm}$
4.  $\frac{\text{Phosphorus mgms. \%} \times 0.6}{\text{mEq/L} \times 1.86} = \text{mOsm}$
5.  $\frac{\text{Glucose mgms. \%}}{18} = \text{glucose in millimols} = \text{mOsm}$
6.  $\frac{\text{Organic Acids in mEq/L} \times 1.86}{\text{Proteins in gms. \%} \times 2.4} = \text{mEq/L} \times 1.86 = \text{mOsm}$
7.  $\frac{\text{Proteins in gms. \%} \times 53.5}{\text{Plasma Albumen in gms. \%} \times 74.4} = \text{colloid osmotic pressure in mm. water (when there is no A/G inversion)}$   
 $\frac{\text{Plasma Globulins in gms. \%} \times 18.9}{\text{Plasma Albumen in gms. \%} \times 74.4} = \text{colloid osmotic pressure in mm. water}$

NaCl is almost completely ionized when in a solution: thus,  $\text{NaCl} \rightleftharpoons \text{Na}^+ + \text{Cl}^-$ , hence, one part or one mol of NaCl yields almost 2 parts of ionic or osmotically active material. The ionization factor is 1.86 for all the electrolytes, therefore mEq/L of an electrolyte multiplied by 1.86 yields the number of milliosmols, mOsm. For non-electrolytes, like urea and glucose, which do not ionize, the concentration in millimols, mM, and mOsm have been considered identical.

The middle part of this chart is a summation of the concentrations of Plasma NaCl, NaHCO<sub>3</sub> and urea, expressed in milliosmols. This graph is recorded in red.

Normal Zone = 215-240 milliosmols.

Attempt should be made to keep the red line within the normal zone by regulating the water, sodium chloride and alkali intake.

On the lower part of the chart is recorded intake and output in 24, or if desired, in 12 hours. Intake by mouth is recorded in black; parenterally in blue. Output—urine in red; drainage, Wangenstein, etc., in green.

Fluid intake should be adjusted to cover adequate urine output, drainage and the insensible water loss. Normally the latter averages 800-1500 cc. but with fever and visible sweating the loss may be 2000-5000 cc. a day.

An output of 500 cc. of urine a day is to be regarded as an absolute minimum; under those conditions the specific gravity should be 1.030 or better. In the event of diminished concentration, with specific gravity around 1.020, the urine output should be maintained at 1000 cc. or better.

I think. So it became a very great burden to the permanent staff to see that these matters of salt and water balance were properly adjusted.

We have felt for some time that we needed a more simple method of recording the pertinent data, something like a temperature chart, something that you could look at and see at a glance whether anything was going wrong,



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without considering separately each item or figure. Then, with the cases that were out of balance you could take the time and trouble to investigate, draw your conclusions and institute the proper treatment. At last, we thought of a graph, you see, something like a temperature chart. You cannot just take the figures of salt and urea and  $\text{CO}_2$  and add them up and build a chart. Urea, for instance, does not ionize; its value as an osmotic agent, therefore, is only about one-half of what salt and bicarbonate is. We needed a common basis for addition, so our biochemist, Doctor Grosscup, suggested expressing these components in milliosmoles, that is, in terms of equivalent osmotic pressure. Hence, we record the sum of the above substances as a red graph, the normal zone of which is between 215 and 240. It is desirable, but not essential, that we understand, in detail, the significance of the figures. As long as we provide for adequate urine output and keep the graphs within or near their normal zones, we have reasonable assurance that the patient's solute and water balance is close to normal. Watch the red line, especially if it is above or below its normal zone—bring it back promptly!

Now, taking a little note from Van Slyke, we say that anything 20 points above or 20 points below indicates a compensated zone but it also indicates danger. Above or below is a signal indicating that the patient is in imbalance and that something must be done at once to restore him. Hence, this is something like a temperature chart. You look at it, your graphs ought to be in their proper zones, and if they are not in there, why not? On the same chart we record in columns in different colors, oral and parenteral intake, also urine output and fluid losses through other channels. This helps to visualize at a glance what is going on. Further, we record the daily intake of glucose and sodium chloride intake and loss. Plasma proteins are estimated whenever indicated since we fully recognize their importance.

In order to have assurance of reasonably accurate collection of specimens and recording data and graphs, we had to put a special metabolic nurse on the job. We detailed her to go around to every tube-case and every case receiving fluids parenterally and see that the nurses were doing their work well. I do not think you are going to get sufficiently accurate data from a changing series of interns. I do not think your chief is going to be able to total these things up himself or herself, and the whole thing will fail unless you build up a mechanism to handle it accurately and without too much trouble.\*

DR. J. SHELTON HORSLEY (Richmond, Va.): The procedure of introducing the Abbott-Miller tube is often very valuable. Of course, it must be applied only in cases of obstruction in which there does not seem to be strangulation of the intestine or a serious affection of its blood supply, as in mesenteric thrombosis. In the type of obstruction following lymphatic adhesions or in adynamic obstruction it is valuable, though in some instances the tube is difficult to introduce.

The presence of an indwelling tube through the nostril, however, is not entirely innocuous, aside from the discomfort that it frequently gives, though in appropriate cases of obstruction these objections must often be endured for the relief that is obtained. Thus, Iglauer and Molt (Iglauer, Samuel, and Molt, Wm. F.: Severe Injury to the Larynx Resulting from the Indwelling Duodenal Tube. *Ann. Otol., Rhinol. and Laryngol.*, **48**, 886, December, 1939) report severe injury to the larynx from an indwelling duodenal tube occurring in ten cases which they have encountered. The tube was in place for periods varying from six to 20 days. Two patients died, and necropsy showed in one of them deep ulceration in the upper end of the esophagus, and in the

\* These charts may be obtained by application to the author, at the Abington Memorial Hospital, Abington, Pa.

other, shallow linear ulcers in the upper end of the esophagus in the cricoid region. Both cases showed marked inflammation in the larynx. In the other patients, a tracheotomy was frequently imperative in order to relieve the acute laryngeal stenosis. They say that tubes of the smallest diameter should be used. Naturally the Abbott-Miller tube cannot be made as small as the Jutte or the Levine tube, so that trauma may be even greater.

Doctor Abbott has shown, in his illustration, that his tube is used after a gastro-enterostomy, being inserted through the nose, into the stomach and into the jejunum so that nourishment can be given.

I wish to call attention to a simple procedure that I have been using for the last few years after pyloroplasty, partial gastrectomy or gastro-enterostomy, which avoids the necessity of having an indwelling tube through the nose. In a gastro-enterostomy, for instance, after the posterior layer of sutures has been placed a sharp-pointed hemostat is introduced through the opening in the stomach and thrust through the anterior wall of the stomach. It catches a medium size soft rubber catheter in which there are two openings. The catheter is clamped about its middle, and is drawn into the stomach for about three inches. It is fastened to the stomach with fine chromic catgut, and around this is placed a purse-string suture of the same material. The gastro-enterostomy is completed, and then a stab wound is made to the left of the abdominal incision and the butt of the catheter is drawn through the stab wound. The stomach is fastened to the parietal peritoneum with fine chromic catgut, and a tag of omentum is also brought around this region.

If it is desired to give nourishment, a longer tube, such as the Jutte tube, can be used instead of the catheter, and can be brought down well into the jejunum.

Thrusting a sharp-pointed hemostat through the stomach wall instead of cutting the stomach does not destroy the muscular layers of the viscus, and when the tube is removed there is usually no leakage of stomach contents. The tube can be kept in indefinitely, and affords not only a means of emptying the stomach contents and relieving the strain on the sutures, but, if placed in the jejunum, may be an avenue of supplying nourishment via the jejunum.

DR. WALTER ESTELL LEE (Philadelphia, Pa.): Doctor Minot has referred to the reactions which follow the use of blood serum, and I would like to call attention to the fact that these reactions are even more severe and more frequent when lyophilized serum is administered intravenously. Doctors Stokes and McGinnis, in the Children's Hospital in Philadelphia, developed, some years ago, a practical method for the preparation of lyophilized blood serum, and they established at the hospital a Bank (which they called a Station) and undertook to supply dried lyophilized serum from the blood of immunes who had had various contagious diseases, such as measles, infantile paralysis, influenza, scarlet fever, *etc.* However, the hopes for this plan have not materialized because it has been found that the reactions were so frequent and severe that the whole scheme has been practically abandoned. Minot has called attention to the fact that these reactions do not occur when plasma is employed instead of sera, and further, that agglutination does not occur with plasma as in serum, which eliminates the necessity for typing and matching of the donor and the recipient. This has been found true not only when the plasma is fresh, but also when it is pooled as a by-product from a Blood Bank. In Philadelphia, we have discontinued the use of whole blood from a Blood Bank after it has reached the age of four days, and the plasma obtained from these Banks has provided a source of supply which, in most hospitals, has been entirely adequate to meet the increasing demands for

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plasma. These demands are increasing rapidly, and, at the present time, in many of the hospitals whole blood is never administered unless there is a specific need for red blood cells. Recently, Doctor Strumia, at the Bryn Mawr Hospital, which is in one of the suburbs of Philadelphia, in reporting his experiences with plasma instead of serum and whole blood, over a period of three or four years, also records his work with lyophilized plasma, the results of which are comparable in every way with those he has obtained with fresh plasma. To us, this seems to be a remarkable contribution, particularly in the present military crisis. The possibility of preparing lyophilized plasma and storing it in glass ampules and shipping it where it may be most needed, would obviate the need for preservation by refrigeration of blood, classification by types, and the cross-matching before a transfusion is administered. The mere mixing of the lyophilized plasma with sterile saline solution will provide a plasma for transfusion which probably will meet the requirements in most of the acute emergencies in military surgery.

DR. A. S. MINOT (Nashville, Tenn., closing): I have listened with interest to the discussions about estimating the need for fluid and electrolyte. I should like to add a suggestion in regard to the estimation of whether or not replacement therapy is keeping up with the loss of plasma volume. When we start to treat a patient we do not know how extensive the capillary damage may be. If it is mainly a question of overcoming dehydration and supplying the necessary fluid and electrolyte, then the intravenous administration of fluid is most valuable in restoring and maintaining the circulation. Under these circumstances the concentration of plasma protein and of cellular elements of hemoglobin should dilute together as fluid is restored. On the other hand, if one makes, as so often happens, the paradoxical observation that the cells are becoming more concentrated in the blood while the plasma protein concentration is progressively decreasing, it can only mean that plasma fluid and protein are being lost from the blood stream. Thus, by making frequent measurements of the hemoglobin concentration and by determining the plasma proteins either chemically or by specific gravity, we have a means of knowing whether the administration of fluid is restoring and increasing the plasma volume or is having the opposite effect. With this information as a guide the replacement therapy can be adapted more closely to the needs of the particular patient.

DR. W. OSLER ABBOTT (Philadelphia, Pa., closing): The question of nasal irritation from the presence of tubes is one which, I think, deserves a word. That is often the factor determining the time for which the tubes can be left in place. Throughout this period, extreme care must be given the nose and throat to keep the mucosa shrunk away from the tube, so that drainage of nasal secretions will be free. Irritation should be relieved, insofar as possible, by the use of local applications. The actual erosion of the nasal pharyngeal surfaces, however, as far as I can determine, occurs more commonly at the time of the withdrawal of the tube than while it is in place, though I say this with the realization that it must in some cases be unavoidable in the course of time. I should like to place the emphasis on careful withdrawal so that the erosions are not produced by actual mechanical friction of the tube through the nasopharynx.

DR. ROBERT ELMAN (St. Louis, Mo., closing): I should like to discuss for a moment Doctor Fine's paper, which I feel is a very important contribution to the treatment of intestinal obstruction. I should like to present one case in confirmation of his findings, with a reversal, however, in the thera-

peutic approach. Doctor Fine remedied the loss of plasma in his patients by correction of the distention; in my case I remedied the distention by correcting the loss of plasma.

Chart 1 represents observations upon a child who was operated upon for rupture of the appendix, with general peritonitis. The recovery following operation was uneventful until the seventh day when she developed abdominal distention and vomited, and, in spite of decompression, remained distended—severely so; more alarming than that, was the general condition of the

Medical No. \_\_\_\_\_

## ST. LOUIS CHILDREN'S HOSPITAL

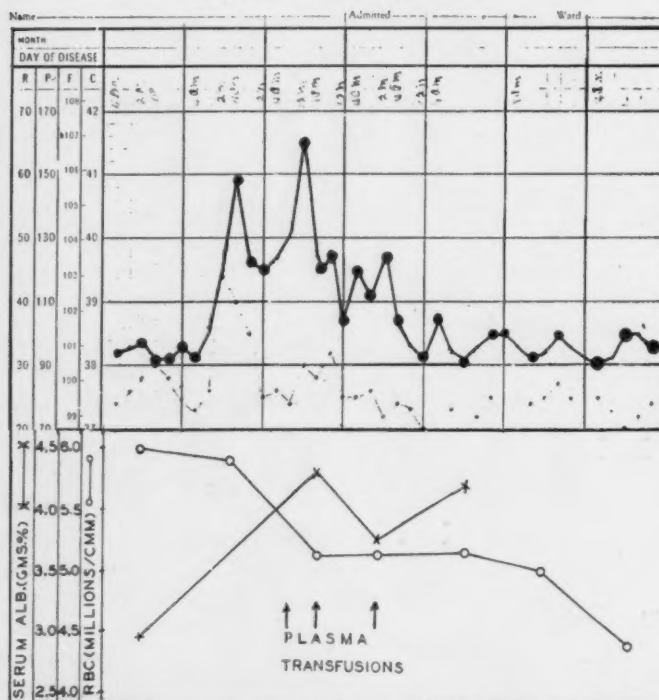


CHART 1.—This represents the findings from the seventh to the fourteenth day following operation for a ruptured appendix, with generalized peritonitis, in a female child weighing 20 Kg. The course was uneventful up to the seventh day, when distention and vomiting began; circulatory collapse developed the next day. Prompt relief following the plasma transfusions (each of 200 cc.) coincided with the return of the various measurements to normal as shown in the chart. In the upper curves the heavy line represents the pulse rate, the light one the temperature; in the lower curves, the red blood count and serum albumin concentrations are indicated in the left margin.

patient which, as indicated by the chart, had produced an extraordinary increase in the pulse rate. She was semicomatose. Her color was poor. The red cell count was 6,000,000; serum albumin, which we feel is more important than the total serum protein, had fallen below 3 Gm. per cent. In spite of the fact that she was receiving the usual amount of parenteral fluid, she excreted but little urine. At the points indicated by the arrow, three plasma transfusions were administered because we felt her dehydration was due to the loss of a great deal of plasma somewhere.

I should like to call your attention to the large dose of plasma that was



given this particular patient. Each injection consisted of 200 cc., which represented 10 cc. per Kg. of body weight, since the child weighed 20 Kg. This same dose was repeated three times within the next 36 hours. This would correspond, in an adult, to the administration of 2,100 cc. of plasma.

The striking thing was the remarkable clinical effect of the plasma transfusions. As can be seen in the chart, there was a fall in the pulse rate; her general condition improved. She became alert. Her color improved. The red count fell promptly, and then became normal. The serum albumin rose to normal (4.3 Gm. per cent). She began to pass flatus and stool, and we were very gratified when the distention disappeared. She recovered completely, without the necessity of any further operative procedure.

This patient, obviously, suffered an extreme degree of plasma loss, the nature of which we were unable to determine, except that, I agree with Doctor Fine, it must have been lost somewhere in the gastro-intestinal tract. Regardless of the cause, however, the result of plasma transfusion in large amounts was a true example of replacement therapy and coincided, in many respects, with the results we have observed with similar treatment in severe cutaneous burns, which was so perfectly, and amply demonstrated by the case which Doctor Minot reported.

DR. CARL W. WALTER (Boston, Mass., closing): I should like to emphasize that solutions which have been prepared properly and sterilized for 30 minutes at 250° F. will keep indefinitely provided they are hermetically sealed. The present, almost universal custom of discarding such solutions after periods of 48 hours to five days is uneconomic, and there is no basis in fact for discarding them.

The second point is that careless sterilization may spoil solutions as far as the clinician is concerned. If the sterilizer operator vents the steam pressure in the sterilizing chamber, solutions at 250° F. are suddenly subjected to atmospheric pressure. Such solutions are then superheated. To relieve this superheat, steam is evolved, and this sudden ebullition of steam causes concentration of the solution. Frequently, the steam in the chamber is vented, while that in the jacket is left on. The solutions are thus gradually boiled away. Accordingly, instead of using isotonic solutions, the clinician may often be using hypertonic solutions. This can be avoided by being certain that the steam supply to the sterilizer is turned off at the end of the sterilizing cycle, and that the autoclave door is securely closed until the temperature of the solution has reached 212° F., where superheat no longer exists and concentration due to evaporation will not occur.



# GASTRIC ACIDITY BEFORE AND AFTER OPERATIVE PROCEDURE WITH SPECIAL REFERENCE TO THE RÔLE OF THE PYLORUS AND ANTRUM\*

A PRELIMINARY REPORT OF A CLINICAL AND EXPERIMENTAL STUDY

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THIS STUDY has as its objective definition of what operative procedure, upon the stomach, accomplishes in the management of duodenal and gastric ulcer. This effort represents an attempt to assay the effects of the commonly practiced operative procedures such as gastro-enterostomy, antral excision and extensive gastric resection upon gastric acidity, and to correlate these findings with the effect of these same operations upon gastric evacuation. The effects of tubular resection with and without gastrojejunostomy and the Schmilinsky operation, in which provision for complete intragastric regurgitation of duodenal content is effected, together with antral excision, upon gastric acidity and evacuation will be reported as well.

Despite studies made upon the physiology of gastric secretion, the factor or factors which determine whether the parietal cells of the acid secreting area of the stomach will or will not secrete free hydrochloric acid remain an enigma still. The importance of acid in the genesis of ulcer has been established definitely by the experiments of Mann and Williamson, and Dragstedt and his associates. Mann and Ivy and their associates, though stressing the importance of the acid factor in the genesis of ulcer, have pointed out repeatedly the importance of the mechanical factor. Moreover, the experiments of Matthews and Dragstedt may be construed to suggest that acid is *the* factor or common denominator of ulcer. The larger number of observers and experimenters are in agreement with Ochsner and his associates that acid is only an important factor in the genesis of ulcer. Other items, such as trauma, the nervous factor and deficiency states, are believed to play a significant rôle.

The operative procedures performed by surgeons for relief of uncomplicated chronic duodenal and gastric ulcer causing pain have largely an empiric

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basis. Through what agency the beneficial effects of operation upon the stomach for ulcer are mediated is still a matter of some speculation and considerable difference of opinion. It is not without interest that the favorable influence of gastro-enterostomy upon a duodenal ulcer has been ascribed successively through the years to: (1) Physiologic rest for the ulcer; (2) improved drainage from the stomach (decreased gastric evacuation time); (3) increased intragastric regurgitation affording opportunity for greater dilution and neutralization of the acid gastric content; and (4) effective reduction of gastric acidity.

Those who advise or practice gastric resection for ulcer set as their objective the attainment of achlorhydria in the residual gastric segment. If the weight of evidence were to be evaluated from the literature in terms of expressions from persons interested and experienced in the field, one would be forced to conclude that the "small gastric resection" (partial), whether performed by the Billroth I or II plan, is an eminently satisfactory operation, insuring achlorhydria—not always but usually achieving this effect through sacrifice of the pylorus and antrum, sometimes described as the acid regulator, awakener or titillator of the acid secreting glands in the corpus and fundus. A large number of surgeons favor the "small gastric resection" (partial) for ulcer. Among others are Friedmann, Fromme, Goetze, Haberer, Hoffman, Könnecke, Lorenz and Schur, Rieder, Rienhoff, and Smidt.

There are, of course, dissenting opinions to this expression. On the one hand, there are those who insist that, whereas antral excision will not insure achlorhydria, a more aggressive excision of the acid secreting area of the stomach will (Finsterer). On the other hand, there are those who suggest that excision of increasingly larger segments of the stomach ("subtotal resection") is not more likely to succeed in making the stomach achlorhydric than is the small gastric resection (partial), and that an extensive gastric resection is just as likely to be followed by an anastomotic ulcer (Shapiro and Berg, and Lewis). The dissenters in this latter group from extensive gastric resection disapprove of the operation for two different reasons: The one, because they feel that the stomach cannot be made achlorhydric as long as any gastric tissue remains; the other, because they feel that gastric resection *per se* is the wrong approach to the whole problem, believing that acid, after all, plays only a small, if any, part in the origins of ulcer (Emery). Others approve of extensive gastric resection for ulcer, but do not believe that gastric acidity *per se* has much to do with the etiology of ulcer (Konjetzny, Mizoguti, and Tomoda and Aramaki). An increasing number of surgeons have found that extensive gastric resection, though not affording the patient absolute protection against recurrent ulcer, is more likely to exhibit fewer failures (A. A. Berg, Finsterer, Graham, Klein, Lahey, Lewisohn, Ogilvie, and Strauss).

Were one of us to set ourselves the laudable task of reading all that has been written upon the mechanism of gastric secretion, the genesis of ulcer and its treatment, a long life of ardent study would not suffice to encompass

the entirety of these intimately related subjects. Moreover, it is even more significant that crucial experiments to secure direct and final answers to these issues have not yet been devised. Ivy, an experienced and successful experimentalist in the field of gastric physiology, said (1931) in a moment of discouragement, "I have been working on the question of ulcer for about 12 years, and I am about to give it up . . . , for the simple reason that I know of no way of producing a pylorospasm or reflex nervous disturbance in a dog, as they are known to occur in man, due to emotions and anxiety with their associated motor and secretory disturbances."

It is obvious that the stomach is a very complex and intricate organ, the functions and mechanisms of which are not wholly understood.

*The Edkins' Hypothesis.*—One of the chief objectives of this study has been to investigate the validity of the Edkins' hypothesis. Pavlov, it is to be remembered, divided gastric secretion into three phases: (1) The psychic or cephalic phase, in which sight, smell or taste of food set up impulses which reach the stomach by way of the vagi nerves, causing a flow of gastric juice. On sham-fed esophagotomized dogs, Pavlov was able to show that vagotomy inhibited psychic secretion of gastric juice. (2) The gastric phase, contingent upon the presence of food in the stomach—elicited by a large variety of foods including water. Whether hydrochloric acid, secreted in response to the presence of food in the stomach, is excited through a secretagogue or hormonal effect is not known. (3) The intestinal phase occasioned by the digestion of food in the intestine and its absorption.

When surgeons adapted gastric resection, which Billroth executed successfully for the removal of gastric cancer, to the surgery of ulcer, it is natural that the same pattern of excision of gastric tissue should have been employed for the management of gastric ulcer. With elaboration of Edkins' hypothesis that gastrin, a pyloric and antral hormone, regulated and controlled the gastric phase of gastric secretion, sufficient justification seemed to have been found for the surgeon's practice of excision of the pylorus and antrum to reduce gastric acidity—a practice which came to be applied later, with even more vigor in certain quarters to the treatment of duodenal ulcer.

The validity of the Edkins' hypothesis of pyloric hormonal control of the gastric phase of gastric secretion is still a matter of no general agreement. Ivy (1930) reviewed the experimental data for and against pyloric hormonal control of the gastric phase of gastric secretion, and concluded that the question could not be answered definitely and finally until it could be determined whether or not purified preparations of gastrin from the antral mucosa were chemically identical with histamine. On the experimental side, too, there is considerable disagreement as to the effect of removal of the pylorus and antrum upon gastric secretion. Among those who insist that results of the sacrifice of the pylorus and antrum in the dog (antral excision plus gastrojejunostomy) uphold the Edkins' hypothesis are Smidt (1923), who observed a shortening of the gastric phase of gastric secretion and a lowering of acidity, and Wilhelmj, and O'Brien and Hill (1936), who observed definite lowering

of gastric acidity. Priestley and Mann (1932), while reporting somewhat inconstant results, concluded that the pyloric mucosa played only a minor rôle in the regulation of gastric acidity. Lewis (1938) excised the antral mucosa, leaving the musculature of this gastric segment intact. He observed marked reduction in gastric acidity, but the response to the histamine test remained normal. Enderlen and Zukschwerdt (1931) demonstrated lowering of gastric acidity in Pavlov pouches in dogs after antral excision, but observed that, in time, the acidity returned to normal. London (1925) has noted this same occurrence.

Portis and Portis (1926), employing a Pavlov pouch, were unable to detect any significant difference in the secretion of the pouch after antral excision. The residual stomach anastomosed to the jejunum they found to be consistently achlorhydric. Shapiro and Berg (1934) confirmed these findings, failing, however, to observe achlorhydria consistently in the residual portion of the stomach anastomosed to the jejunum. The observations of Steinberg, Brougher and Vidgoff (1927) are in general agreement with those of Portis and Portis, and Shapiro and Berg—all of which tend to discredit the Edkins' hypothesis, as well as the practice of antral excision, as an effective means of reducing gastric acidity in the management of ulcer.

On the clinical side, however, as indicated above, expressions from those who have applied the Edkins' hypothesis to ulcer management suggest quite strongly that antral excision is an effectual and satisfactory means of reducing gastric acidity.

*The Authors' Approach to the Problem.*—In essaying to evaluate the accomplishments of operation in the management of ulcer, as well as the manner in which the effects of operation are mediated, we have regarded surgical therapy as an experimental approach to the ulcer problem. A most conservative attitude regarding the rôle of surgery in the management of ulcer has been entertained by both internists and surgeons in the clinics of the University Hospital. Up until recently, gastro-enterostomy was the commonly practiced operative procedure in those patients presenting classic and somewhat pressing indications for operations, save for the gastric ulcer which was suspected of being malignant. Gastric resection has been performed regularly for gastric ulcer when the roentgenographic defect persisted despite rigidly controlled dietary management and bed rest. With some mutual misgivings, entertained by both internists and surgeons over the accomplishments of gastro-enterostomy and with the consent of the Department of Medicine, the surgical staff, while still adhering strictly to orthodox indications for operation, chose to vary the type of surgical procedure, with the consideration in mind of garnering useful information concerning the rôle of various operations in the management of ulcer, as well as the manner in which such influence is mediated.

In addition, in the laboratory a variety of experimental procedures have been carried out, largely upon the dog, in an attempt to assay further the validity of the Edkins' hypothesis. These experiments will be cited briefly



here, together with some work still in the process of prosecution which lends increased credence to the significance of acid as a most important factor in the genesis of ulcer, as suggested in the experiments of Mann and Williamson, and Matthews and Dragstedt.

*The Clinical Data.*—It was the occurrence of gastrojejunal ulcer in two patients, subjected to antral resection because of continued bleeding from a duodenal ulcer, that suggested this study. Both patients (Cases 1 and 2, Table II) had had a previous gastro-enterostomy, and when the antral resection was performed, no evidence of a gastrojejunal ulcer was observed in either instance. In both patients, gastrojejunal ulcer followed antral excision within a few months.

Sixty patients having the following types of operative procedure were available for study:

Group I: Twenty-nine cases gastrojejunostomy—retrocolic.

Group II: Six cases antral excision, with complete terminolateral anastomosis (Pólya).

Group III: Ten cases extensive gastric resection including pylorus and antrum, with either partial (Hofmeister) or complete retrocolic terminolateral anastomosis (Pólya). Entero-anastomosis was performed in some; in others it was omitted.

Group IV: Six cases antral exclusion, with extensive gastric resection (Finsterer's operation) accompanied either by partial (Hofmeister) or complete retrocolic terminolateral anastomosis (Pólya). Entero-anastomosis was more often performed than omitted. This operation was undertaken in instances of duodenal ulcer with choledochoduodenal fistula and in other instances of duodenal ulcer in which there was a good deal of induration of the duodenum, extending in a few instances into the prepyloric region. The segment of stomach remaining proximal to the pylorus followed in all instances Finsterer's admonition of leaving not more than two fingers' breadth of gastric tissue.

Group V: Three cases—provision for complete intragastric regurgitation for gastrojejunal ulcer following antral excision (Schmilinsky operation). Cases 1 and 2 of this group appear also in Group II.

Group VI: Five cases tubular excision (fundus and corpus) with gastrojejunostomy, leaving the antrum and pylorus intact.

Group VII: Three cases tubular excision (fundus and corpus) without gastrojejunostomy, leaving the antrum and pylorus intact.

In those instances operated upon within the last year, careful note was made of the amount of gastric tissue excised at operation. In the earlier cases, extensive gastric resection was performed for high-lying gastric ulcer; in duodenal ulcer, gastro-enterostomy was the common operative procedure. Antral excisions were done for bleeding duodenal ulcer and the occasional gastric ulcer situated near the pylorus.



In all patients, carefully controlled postoperative studies of gastric acidity have been made. In most patients, including all the resections, such preoperative data are available. The postoperative observations made upon these patients include: (1) Studies of gastric acidity; (2) gastric emptying time, employing the neutralization test (introduction of 150 cc. of 0.4 per cent HCl into the stomach); and (3) gastric evacuation time, determined fluoroscopically, after the patient swallowed 150 cc. of a thin barium mixture. The emptying time for barium was 83 minutes in a small group of normal persons (Bergh).

The gastric acidity was determined by the usual colorimetric titration, employing Töpfer's reagent as the end-point for free hydrochloric acid and phenolphthalein as the end-point for the total acid.

Gastric acidity was determined regularly in the morning, the patient having had no breakfast. A No. 14F. duodenal tube with four perforations at the tip was introduced through the nose into the stomach, and periodic aspirations were made as follows: (1) Fasting; (2) 30 minutes after intragastric instillation of alcohol (50 cc. of 7 per cent solution); and (3) 30, 60 and 90 minutes after 0.5 mg. of histamine hydrochloride.\* In the "neutralization test," acid was introduced into the fasting stomach and aspirations were made at subsequent intervals of 15, 30, 45, 60, 75 and 90 minutes. The figures in the table indicate the amount of acid "neutralized or lost" in one hour. In the graphic sketches of the results of this test, we have employed the normal standard described by Elman. This test is probably described more accurately as a test of the gastric evacuation time. Control studies with barium suggest a fairly close parallelism between the ability of the stomach to "neutralize" acid and rapid evacuation. That is, a stomach that emptied rapidly with barium also showed a great capacity to "neutralize" acid introduced. We have come to speak, therefore, of acid loss, through rapid gastric emptying rather than neutralization.

We have chosen to put a good deal of emphasis upon the results of the histamine (maximal) stimulation, feeling that these findings are most significant. It is to be admitted freely that histamine, in a sense, is not a physiologic activator of gastric secretion. That is, histamine does not give a maximal stimulus alike to the secretion of pepsin and mucus, as it does to hydrochloric acid. Yet, the subcutaneous injection of histamine evokes the maximal known stimulation of acid secretion from the gastric glands and constitutes, therefore, a real test of the ability of operative procedures to make the stomach achlorhydric. It might reasonably be asked whether one should not regularly expect evidence of active secretion of hydrochloric acid after histamine, as long as any normal gastric tissue remained, no matter what type of operative procedure had been performed. Interestingly enough, however, as the data will indicate, the procedure and the amount of tissue removed have an important answer to give to this question.

\* One-half milligram of histamine hydrochloride represents 0.3 mg. of histamine base.

The data are summarized briefly in tables corresponding in number to the groups listed above.

TABLE I  
PATIENTS HAVING GASTROJUNOSTOMY

Name Hosp. No. Age—Diag. Oper.— Date	Date of Analysis	Fasting Free Acid	Maxi- mum Free with Hista- mine	Maxi- mum Total with Hista- mine	Volume of Secre- tion $\frac{1}{2}$ hr. (in Cc.)	Acid Output Mg. $\frac{1}{2}$ hr.		Acid Neu- tralized % Acid Loss	Mo- tility Emp- tying Time —Ba.
(1) Mrs. L. L.* 685777 59—D.U. G.J.—9/6/20	10/24/39	0	0	32	12.0	0	14.0	93	
(2) Mr. H. H. 690290 40—D.U. G.J.—1927	1/23/40	20	8	32	18.0	5.0	21.0	94	195 min.
(3) Mr. A. S. 656876 55—G.U. and D.U. G.J.—1927	3/18/40	0	84	102	9.0	27.6	32.2		60 min.
(4) Mr. E.F. 617977 54—D.U. G.J.—8/28/33	2/27/40	32	34	54	11.0	13.6	21.6	90	
(5) Mrs. J. R. 606079 62—D.U. G.J.—3/23/34	2/6/40 4/17/40	14 40	80 57	96 67	3.5 4.7	10.3 9.0	12.3 10.0	94	30 min.
(6) Mr. R. Z. 674760 60—D.U. G.J.—4/1934	2/32/40	12	56	74	18.0	36.8	48.6	93	60 min. 15 min.
(7) Mr. V. C. 624155 67—D.U. G.J.—7/25/34	1/22/34 1/27/34 11/10/39 2/8/40	51 12 + 60	 50 0 37.5	66 28 77.5	 9.0 4.6	 0 6.3	 18.4 13.5	100 98	
(8) Mrs. A. S. 630909 38—P.U.† G.J.—10/12/34	9/8/34 11/12/39 2/29/40 4/4/40 4/27/40	0 0 0 0 0	 0 0 0 0†	28 36 20 40½	13.4 2.7 2.0 1.2	0 0 0 0	13.5 3.6 1.46 0	88 79	40 min.
(9) Mr. H. M. 617859 31—J.U. G.J.—1/2/35	11/7/39	0	50	62	14.3	25.5	31.0		

# PRE- AND POSTOPERATIVE GASTRIC ACIDITY

TABLE I (Continued)

Name Hosp. No. Age—Diag. Oper.— Date	Date of Analysis	Fasting Free Acid	Maxi- mum Free with Hista- mine	Maxi- mum Total with Hista- mine	Volume of Secre- tion $\frac{1}{2}$ hr. (in Cc.)	Acid Output Mg. $\frac{1}{2}$ hr.		Acid Neu- tralized % Acid Loss	Mo- tility Emp- tying Time —Ba.
(10) Mrs. J. F. 641350 71—D.U. G.J.—10/15/35	2/21/40	13.5	50	60	22.0	40.0	48.0	86	115 min.
(11) Mrs. R. S. 620111 66—D.U. G.J.—10/18/35	3/6/40	0	62	72	7.0	15.6	18.4	87	80 min. (95%) empty
(12) Mr. F. M. 645426 69—G.U. G.J.—7/28/36	2/21/40 4/4/40 4/17/40	0 0 24	0 50 34*	22 62 44‡	9.8 6.2 13.0‡	0 11.2 16.2	7.8 15.0 21.0	98	60 min.
(13) Mrs. C. H. 652147 55—G.U. G.J. 9/30/36	1/15/36 5/9/38 2/6/40	0 0 50	62 78 98	80 98 110	13.0 6.0 14.0	29.4 17.1 50.2	37.8 21.6 56.0	69	60 min.
(14) Mr. W. P. 655113 42—D.U. G.J.—1/11/37	3/25/40	62	116	132	17.0	72.0	82.0		95 min.
(15) Mr. J. J. 656061 32—D.U. G.J.—6/9/37	2/20/37 2/26/40	0 24	0 46	12 58					
(16) Mr. F. W. 661275 40—D.U. G.J.—6/1937	2/29/40 4/9/40	0 50	0 72	100 80	0.5 30.0	0 78.4	1.8 87.4	98	95 min.
(17) Mr. W. P. 659592 50—D.U. G.J.—8/18/37	2/19/40 4/26/40	15 0	32 50	44 60	5.0 28.0	5.8 51.0	8.0 61.0		15 min.
(18) Mr. O. W. 661145 60—D.U. G.J.—9/9/37	2/19/40	60	82	98	26.0	78.0	93.2		
(19) Mr. C. W. 659895 56—G.U. G.J.—9/9/37	6/24/37 12/8/39 2/8/40	20 0 64		36 68 56	3.1 4.0	3.8 5.8	7.5 8.1	97 93	12 min. 15 min. 14 min.

TABLE I (Continued)

Name	Hosp. No.	Age—Diag.	Oper.— Date	Date of Analysis	Fasting Free Acid	Maxi- mum Free with Hista- mine	Maxi- mum Total with Hista- mine	Volume of Secre- tion $\frac{1}{2}$ hr. (in Cc.)	Acid Output Mg. $\frac{1}{2}$ hr.		Acid Neu- tralized % Acid Loss	Mo- tility Emp- tying Time —Ba
									Free	Total		
(20)												
Mr. J. K.				2/16/38	0	20	30	9.0	6.5	9.2		
666254				11/8/39	12	74	92	14.0	37.6	30.0	89	
58—D.U.												
G.J.—3/3/38												
(21)												
Mr. M. B.				2/8/40	48	50	68	14.0	25.5	34.6	92	3 hr. 30 min.
636231												(65% empty)
55—D.U.												
G.J.—11/25/38												
(22)												
Mr. R. M.*				2/21/40	0	0	16	3.0	0	1.75	96	30 min.
637026												
39—D.U.												
G.J.—12/19/38												
(23)												
Mr. L. J.				2/7/40	68	84	94	16.0	49.0	54.0	86	40 min.
672742												
30—D.U.												
G.J.—12/28/38												
(24)												
Mr. A. W.				5/12/36	37							
648654				1/29/38	21	71	80	17.0	44.0	49.5		
54—D.U.				4/25/39	0	8	18					
Perf. sutured				11/8/39	38	28	44	47.0	47.0	75.0		
7/28/37				3/5/40	18	0	18	11.0	0	7.2	100	85 min.
G.J.—1/31/39												
(25)												
Mr. O. N.				5/8/38	24							
668719				6/22/39	0							
73—G.U.				10/24/39	0	0					94	
G.J.—7/13/39				12/28/39	0	0	55	1.9	0	3.0	97	30 min.
				3/29/40	0	0	22	4.1	0	3.2		80 min.
				4/16/40	0	32 $\frac{1}{2}$	40 $\frac{1}{2}$	7.2	8.3	10.4		
(26)												
Mr. R. E.				2/19/40	0	10	18	12.0	4.4	7.9	96	1 hr.
672523				4/15/40	22	76*	92*	10.0	27.0	33.0		
29—D.U.												
G.J.—10/25/39												
(27)												
Mr. W. W.*				10/31/39	28	86	100	67.0	210.0	248.0	42	
686536				11/20/39	0	0	25	10.6	0	9.2	97	
51—G.U.				11/22/39	0							
G.J.—11/6/39				11/25/39		0	40	67.0	0	97.0		
(28)												
Mr. H. E.				12/21/39	64	96	110	15.0	52.0	61.0	90	
688048				1/20/40	0	25	55	4.6	4.7	10.2	83	
38—D.U.				1/22/40	12	38	78	7.0	9.6	20.0	96	
G.J.—12/21/39												

# PRE- AND POSTOPERATIVE GASTRIC ACIDITY

TABLE I (Continued)

Name	Amount Resected	Date of Analysis	Pasting Free Acid	Maximum Free with Histamine	Maximum Total with Histamine	Volume of Secretion ½ hr. (in Cc.)	Acid Output (Histamine) Mg. ½ hr.		Acid Neutralized % Acid Loss	Motility Emptying Time —Ba.
Hosp. No.	(in sq. cm.)						Free	Total		
Age—Diag.										
Oper. Date										
(29)										
Mrs. D. V.	12/31/39	20	65	73	18.0		42.0	48.0	77	
686531	1/2/40	0								
50—D.U.	2/5/40	0	38	62	20.0		27.4	45.0	86	
G.J.—12/22/39	4/26/40	16	22‡	32†	18.0		14.4	21.0		

\* Not available for verification with triple histamine.

† Possibly luetic gastritis.

‡ Specimens taken 30 minutes after three successive injections of 0.5 mg. of histamine.

Abbreviations: G.U. = gastric ulcer.

D.U. = duodenal ulcer.

P.U. = pyloric ulcer

G.J. = gastrojejunostomy

## RESULTS

### GROUP I—GASTROJEJUNOSTOMY

It is to be noted that the reduction in gastric acidity after gastrojejunostomy is slight. There are a few patients who have been achlorhydric, at least on one occasion. However, *not a single patient* with a well-authenticated record of ulcer has been achlorhydric after the administration of 1.5 mg. of histamine in triple doses of 0.5 mg. given one-half hour apart. These findings confirm the statement of Holman and Sandusky, who found that achlorhydria was a rare occurrence after gastrojejunostomy for ulcer.

That a number of patients having gastrojejunostomy became free of symptoms is well known and suggests that the operation has some virtue. The rapid loss of hydrochloric acid from the stomach in the neutralization test and the decreased emptying time with barium suggest that the value of gastrojejunostomy lies in the more rapid emptying of the stomach (Fig. 1).

### GROUP II—EXCISION OF ANTRUM AND PYLORUS

There are six patients in this group. Without exception, all these patients had their operation for massive hemorrhage from duodenal ulcer. In four instances, a preliminary gastrojejunostomy was performed. In all instances, save the first, the interval between gastrojejunostomy and excision of pylorus and antrum was only a few days to a few weeks or months. In the first patient in the group, the interval between gastrojejunostomy and excision of the pylorus and antrum was more than 12 years. In this patient, unfortunately, no studies of gastric acidity were made until several months after the Schmilinsky operation had been performed for gastrojejunal ulcer occurring after antral excision.

This patient has exhibited achlorhydria occasionally after histamine. As recently as September, 1939, almost four years after the Schmilinsky operation, he was still not achlorhydric on histamine stimulation. After the administration of triple doses of 0.5 mg. of histamine given at intervals of half an hour, gastric analysis showed free hydrochloric acid to be present. One other



TABLE II

PATIENTS HAVING EXCISION OF ANTRUM AND PYLORUS\*

*Small Gastric Resection**All Complete Terminolateral Anastomoses—No Entero-anastomoses*

Name	Amount Resected (in sq. cm.)	Date of Analysis	Fasting Free Acid	Maximum Free with Histamine	Maximum Total with Histamine	Volume of Secretion ½ hr. (in Cc.)	Acid Output (Histamine) Mg. ½ hr.		Acid Neutralized % Acid Loss	Motility Emptying Time —Ba.
Hosp. No.	Age—Diag.	Oper. Date					Free	Total		
(1)										
Mr. F. F.†		5/29/34	7	8	16					
627911		4/19/35	16	70	82	67.0	175.0	198.0		
49—D.U.		12/31/36	0	0	23					
G.J.—1918.		9/5/39	0	9	39	12.0	5.9	26.0		
Ant. Resect.		3/11/40	0	0	30	16.0	0	13.0		160 min.
4/20/35.										
Schmilinsky										
1/8/36										
(2)										
Mr. C. M.		1/20/34	0	53	63					
623906		11/11/36	0	0	32	20.0	0	23.2		
49—D.U.		11/14/36	13	0	20	1.5	0	2.11	100	
G.J.—11/14/38		2/26/40	0	34	52	13.0	15.0	25.0	95	30 min.
Ant. Resect.		4/4/40	30	68	72	.31	7.7	8.1		
12/17/38	138									
(3)										
Mr. L. K.‡		5/25/38	30							
669044		6/13/38		80	100					
24—D.U.		4/18/39	52							
G.J.—2/14/39		5/8/39	0	38	50	9.0	12.3	16.4		
Ant. Resect.		5/15/39	31							
2/21/39.										
Schmilinsky		6/28/39	24							
with excision		8/29/39	0	26	40	15.0	14.3	22.0		
of a portion										
of fundus										
5/15/39	110									
(4)										
Mr. L. W.		8/29/39	24	**	71					
643715		11/8/39	0	0	60	2.0	0	4.3	58	
50—D.U.		2/21/40	0	18	36	11.0	7.24	14.3	79	155 min.
9/3/39	130	4/10/40	0	0	24	12.0				
		4/22/40	0	18½	65½	1.7	1.1	4.0		
(5)										
Mr. C. B.		7/10/39	27	**	**					
642665		11/14/39	24	56	88	3.7	7.0	11.8	82	40 min
41—D.U.		2/15/40	20	56	64	22.0	45.0	51.0	84	
G.J.—3/20/39.										
Ant. Resect.	143									
7/10/39										
(6)										
Mr. G. A.		6/28/39	15	82	91	12.0				
661081		9/30/39	0	62	78	35.0	79.0	100.0	72	310 min.
56—D.U.		11/7/39	0	40	116	90.0	135.0	384.0	18	145 min.
9/18/39	117	4/23/40	66	100	122	12.0	43.8	53.0		

\* All patients in this group were operated upon for massive hemorrhage from duodenal ulcers.

† Case 1, Table IV.

‡ Case 2, Table V.

§ Specimens taken 30 minutes after three successive injections of 0.5 mg. of histamine.

|| This patient has also a stricture of the lower esophagus from "acid ulceration" of the esophagus.

\*\* Operated upon as an emergency for massive hemorrhage threatening life. No preoperative determinations of acid were made.

# PRE- AND POSTOPERATIVE GASTRIC ACIDITY

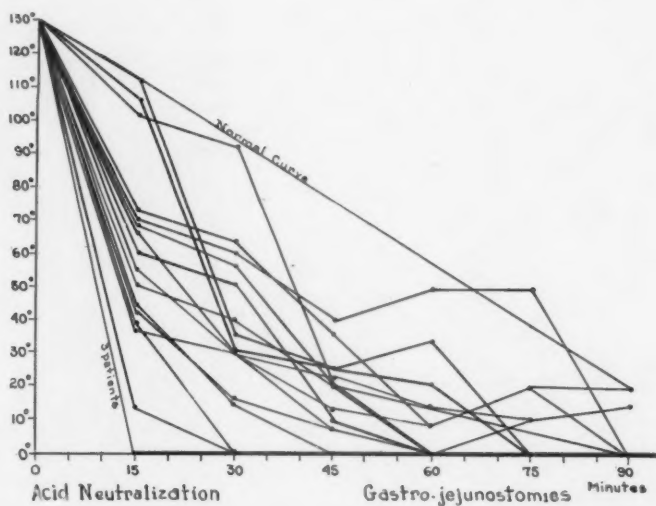


FIG. 1.—Decreased evacuation time of the stomach occurring after gastrojejunostomy, as indicated by the ability of the stomach to "neutralize" acid. The straight line of the normal curve is that previously employed by Elman (1929).

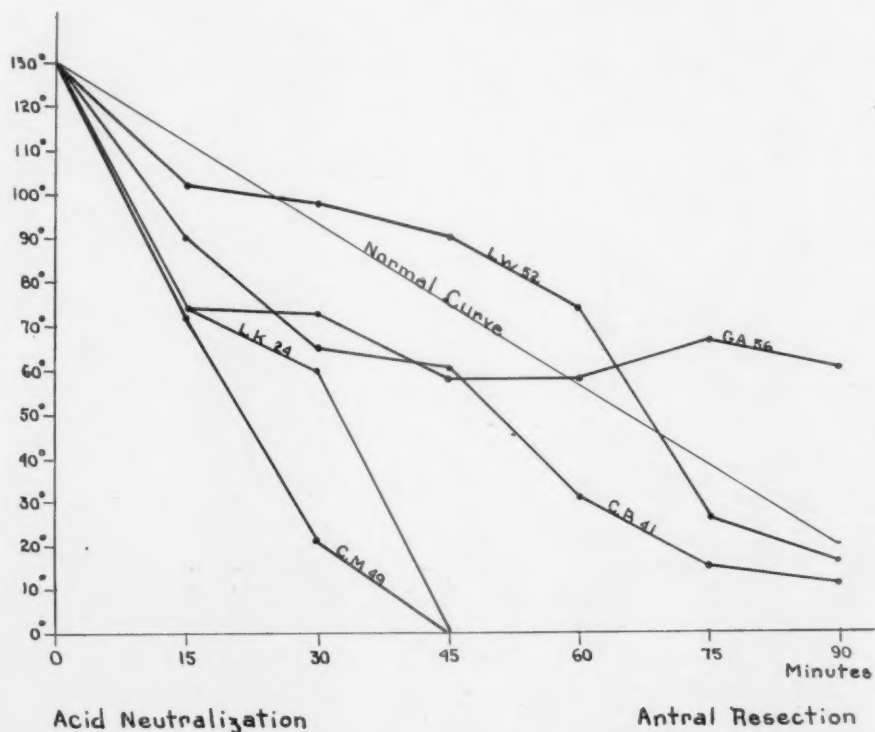


FIG. 2.—Gastric evacuation time as indicated by acid neutralization after antral resection.

TABLE III

EXTENSIVE GASTRIC RESECTION INCLUDING EXCISION OF PYLORUS AND ANTRUM\*

Name Hosp. No. Age—Diag. Oper. Date	Amount Resected (in sq. cm.)	Date of Analysis	Fasting Free Acid	Maxi- mum Free with Hista- mine	Maxi- mum Total with Hista- mine	Volume of Secre- tion ½ hr. (in Cc.)	Acid Output (Histamine) Mg. ½ hr.		Acid Neu- tralized. % Acid Loss	Mo- tility Emp- tying Time —Ba.
(1)										
Mr. G. T. 48237		6/15/29 6/24/29	26 26							
58—G.U. 7/3/29		11/9/39	0	0	38	11.0	0	15.0	90	
(2)										
Mrs. A. K. 53599		4/10/40	0	0	12	3.2	0	1.4		
63—G.U. 4/21/30										
(3)										
Mr. A. F. 604349		1/25/32 3/14/40	49 0	77 0	93 22	78.0 17.0	219.0 0	264.0 13.6		15 min.
42—D.U. G.J.—1916. Reop. G.J.—1929 2nd G.J.—1930 2/29/32										
(4)										
Mr. M. S. 625719		3/20/34 6/11/35	41 44	37 30	51 54					
44—G.U. and D.U. 6/18/35		10/24/39 3/18/40 4/27/40	0 0 0	0 84 0†	36 102 30†	5.0 22.0 9.0 1.1	5.44 0 27.0 0	9.9 28.9 33.0 0	90	45 min.
(5)										
Mr. W. R. 654309		5/5/38 4/3/39	20 0	45 20	52 24	15.0 8.0	17.5 5.8	35.0 7.0		
49—G.U. 3/24/39	200	5/23/39 6/6/39 10/18/39 2/20/40 4/11/40	0 0 8 0 0	0 0 0 0 15†	8 18 20 16 45†					
									93 94 94	10 min.
(6)										
Mr. W. S. 586233		12/30/39 1/3/40	26 0	36 14	63 32	19.5 18.0	26.0 9.2	46.0 21.0	54 100	
67—G.U. 1/4/40	178	1/17/40 4/11/40	0 0	0 0	20 37.5	12.7 4.4	0 0	9.0 5.9	96	5 min.
(7)										
Mr. H. P. 691274		2/1/40 3/8/40	0 0	0 0	14 32					
53—G.U. 2/27/40	295	4/11/40	0	0†	32†	9.0 7.5	0 0	10.5 8.7		9 min.
(8)										
Mrs. E. F. 693430		3/25/40 4/8/40	0 0	0 0†	37.5 40†	0.15 0.5	0 0	0.19 0.7		Unable to tol- erate 150 cc. Stom- ach empties imme- diately
57—D.U. and G.J.U. G.J.—20 yrs. ago 3/13/40	201§	4/24/40	0	0	40	3.0	0	4.3		

## PRE- AND POSTOPERATIVE GASTRIC ACIDITY

TABLE III (Continued)

Name	Amount Resected (in sq. cm.)	Date of Analysis	Fasting Free Acid	Maxi- mum Free Hista- mine	Maxi- mum Total with Hista- mine	Volume of Secre- tion ½ hr. (in Cc.)	Acid Output (Histamine) Mg. ½ hr.		Acid Neu- tralized. % Acid Loss	Mo- tility Emp- tying Time —Ba.
(9)										
Mr. F. V.†		4/11/40	32	72	92	33.0	85.4	111.0		
694465		4/22/40	0	0	58	7.5	0	16.0		
68 G. U.										
4/12/40	274									
(10)										
Mr. M. M.		4/14/40	0	94	122	132.0	413.6	530.0		
694565		2/26/40	0	10	32	15.0	8.7	17.5		
45—prepyloric ulcer										
4/18/40	310									

\* Cases 1, 2, 3, 4, 5 and 6 had complete terminolateral anastomoses.

Cases 7, 8, 9 and 10 had partial inferior terminolateral anastomoses.

Cases 1, 3, and 4 had no entero-anastomosis. All other cases had entero-anastomoses.

† Specimens taken 30 minutes after three successive injections of 0.5 mg. of histamine.

‡ This patient had two lesions: An ulcer on the lesser curvature and a small carcinoma in the pyloric region. The lesions were definitely independent of one another.

§ Area determined after the specimen had been in the refrigerator for a few hours—this measurement, therefore, does not take into account the contraction that occurred. Patient operated upon as an emergency for acute, massive hemorrhage from gastrojejunal ulcer—consequently no preoperative determinations of gastric acidity.

patient in this group (Case 4) has been achlorhydric, even to histamine stimulation. After three doses of 0.5 mg. of histamine given consecutively over half-hour intervals, however, free hydrochloric acid appeared in the gastric secretion. None of the other patients in the group are achlorhydric to histamine, though Case 6 has been achlorhydric, fasting. It is apparent that removal of the antrum and pylorus is an unsatisfactory operation to reduce gastric acidity (Fig. 2). The rapid emptying observed after gastrojejunostomy was noted also in this group. Two of these six patients (Cases 1 and 3) also developed gastrojejunal ulcer, which neither patient had after gastrojejunostomy alone. With the exception of the patients who developed gastrojejunal ulcer, the others are well. The two who developed gastrojejunal ulcer (Cases 1 and 3) will be discussed again under Group V.

#### GROUP III—EXTENSIVE GASTRIC RESECTION INCLUDING EXCISION OF ANTRUM AND PYLORUS

There are ten patients in this group. The matter of the size of the resection will be discussed in a separate section. All patients in this group have been achlorhydric to histamine at times. However, none have been consistently achlorhydric. The lapse of time is apparently a factor in establishing achlorhydria (Cases 5 and 6). In the first four cases in the group, the first analysis of gastric acidity after operation, made after the lapse of months or years, demonstrated achlorhydria regularly. We have since learned that it is im-

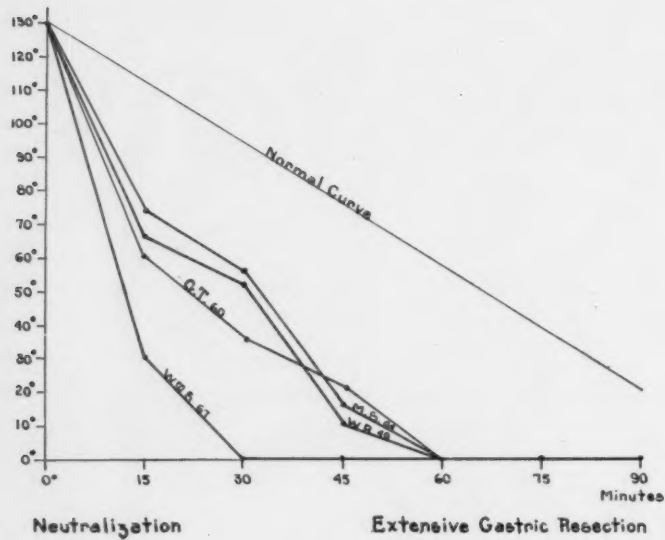


FIG. 3.—Gastric evacuation time as indicated by acid neutralization after extensive gastric resection (Cases in Group III).

#### Types of Operative Procedure

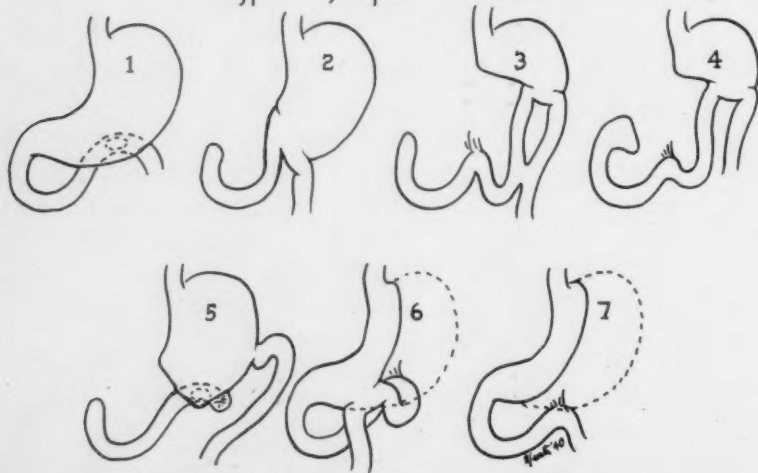


FIG. 4.—Various types of operative procedures employed in the cases listed in the tables:

1. Gastrojejunostomy.
2. Antral resection.
3. Extensive gastric resection. Some patients had entero-anastomosis—others did not.
4. Extensive gastric resection accompanied by antral exclusion (Finsterer). Some patients had entero-anastomosis—others did not.
5. Schmilinsky procedure providing total intragastric regurgitation.
6. Tubular resection with gastrojejunostomy, leaving pylorus and antrum intact.
7. Tubular resection without gastrojejunostomy, leaving pylorus and antrum intact.



## PRE- AND POSTOPERATIVE GASTRIC ACIDITY

TABLE IV  
EXTENSIVE GASTRIC RESECTION LEAVING THE PYLORUS AND A SMALL SEGMENT  
OF THE ANTRUM\**Antral Exclusion Operation of Finsterer*

Name	Amount Resected (in sq. cm.)	Date of Analysis	Fasting Free Acid	Maxi- mum Free with Hista- mine	Maxi- mum Total with Hista- mine	Volume of Secre- tion $\frac{1}{2}$ hr. (in Cc.)	Acid Output (Histamine) Mg. $\frac{1}{2}$ hr.		Acid Neu- tralized % Acid Loss	Mo- tility Emp- tying Time —Ba.
							Free	Total		
(1)										
Mr. P. M.		4/20/37	14							
658072		6/6/39	0	0	18	10.0	0	6.5	98	10 min.
38—D.U.		2/14/40	0	0	16	3.5	0	2.1	97	
G.J.—5/1933										
5/13/37										
(2)										
Mrs. M. B.		10/14/39	54							
686389		2/18/40	42							
36—G.U.		3/7/40	0	0	44	4.3	0	6.9		30 min.
2/26/40	225	4/16/40	0	30†	40†	11.0	12.0	16.0		
(3)										
Mr. J. E.		3/2/40	50	64	84	55.0	138.0	168.0		
684691		3/19/40	0	26	32	30.0	28.0	28.6		
38—D.U.		4/9/40	8	0	20	11.0	0	8.0		120 min.
3/8/40	258									
(4)										
Mr. E. H.		2/27/40	0	0	28	2.6	0	2.6	80	
685488		3/27/40	90	122	128	30.0	124.0	140.0		
40—D.U.		4/15/40	12	38	58	19.0	26.0	40.2		60 min.
4/3/40	301	4/22/40	0	56	144	2.6	5.3	13.6		
(5)										
Mr. C. S.		4/2/40	36	86	94	12.0	37.5	41.0		
694074		4/20/40	0	0	24	11.0	0	9.6		35 min.
24—D.U.		4/22/40	0	17.5	42.5	5.0	3.0	7.8		
4/11/40	244									
(6)										
Mr. T. B.		3/29/40	14							
694134		3/30/40	8							
40—D.U.		3/31/40	44							
4/15/40	224	4/11/40	93							
		4/15/40	106							
		4/22/40	40	70	100	18.0	46.0	62.0		
		4/26/40	36	72	94	51.0	133.0	174.0		

\* Complete terminolateral anastomoses in Cases 1 and 2. Partial, inferior terminolateral in the others. Entero-anastomoses in all but Case 1.

† Specimens taken 30 minutes after three successive injections of 0.5 mg. of histamine.

portant to make observations beginning early in the recovery period to determine when achlorhydria supervenes. Now, save with employment of triple 0.5 mg. doses of histamine, all but the last patient in the series (Case 10) is achlorhydric to the usual 0.5 mg. dose of histamine.

The emptying of the stomach in this group, in all instances in which the examination has been made, is very rapid (Fig. 3). All patients in the group are symptomatically well. There have been no gastrojejunal ulcers.

## GROUP IV—EXTENSIVE GASTRIC EXCISION WITH EXCLUSION OF THE PYLORUS AND ANTRUM (FINSTERER OPERATION)

This type of operation is indicated particularly in duodenal ulcer complicated by choledochoduodenal fistula, or when there is considerable edematous induration of the duodenum, pylorus and antrum. The admonition, of Finsterer, to leave only a portion of the antrum, lest the acid secreting cells

TABLE V  
PATIENTS HAVING THE SCHMILINSKY OPERATION FOR GASTRO-JEJUNAL ULCER  
(Provision for Complete Intra-gastric Regurgitation)

Name Hosp. No. Age—Diag. Oper. Date	Amount Resected (in sq. cm.)	Date of Analysis	Fasting Free Acid	Maxi- mum Free with Hista- mine	Maxi- mum Total with Hista- mine	Volume of Secre- tion ½ hr. (in Cc.)	Acid Output (Histamine) Mg. ½ hr.		Acid Neu- tralize % Acid Loss	Moti- lity Emp- tying Time —Ba.
(1)										
Mr. F. F.		5/29/34	7	8	16					
627911		4/19/35	16	70	82	67	175.0	198.0		
49—D.U.		12/31/36	0	0	23					
G.J.—1918.		9/5/39	0	9	39	12	5.9	26.0		
Ant. Resect.		3/11/40	0	0	30	16	0	13.0		160 min.
4/20/35.										
Schmilinsky										
1/8/36										
(2)										
Mr. L. K.*		5/25/38	30							
669044		6/13/38		80	100					
24—D.U.		4/18/39	52							
G.J.—2/14/39.		5/8/39	0	38	50	9	12.3	16.4		
Ant. Resect.		5/15/39	31							
2/21/39.										
Schmilinsky	110	6/28/39	24							
with excision of a portion of fundus		8/29/39	0	26	40	15	14.3	22.0		
5/15/39										
(3)										
Mr. A. S.†		9/5/35	69							
641802		4/7/39	27							
35—D.U.		4/14/39	89							
G.J. 1/1938.		4/24/39	16	22	40	25	20.0	36.5		
Excision of gas- trojejunal ul- cer and exclu- sion of greater curvature	214	5/24/39	32							
4/14/39.		6/22/39	0	56	60	6	12.2	13.0		
Schmilinsky		7/15/39	0	42	94	11	16.8	37.6		
with excision of a portion of fundus and antrum	125	9/28/39	5	0	21	52	0	39.9		
8/14/39										

\* Died at home, suddenly, 9/16/39, four months after the Schmilinsky operation of perforation of a new, acute gastrojejun ulcer in the new stoma. Autopsy courtesy Dr. B. O. Mork, Jr., Worthington, Minn.

† Died in hospital, 10/8/39, 52 days after the performance of Schmilinsky operation, of uncontrollable gastric hemorrhage. A large, shallow autolytic ulcer of the stomach was found—gastrojejun ulcer healed.

of the corpus be allowed to remain behind distal to the site of section and inversion of the stomach, has been observed. The upper site of section remains the same as for the ordinary extensive gastric resection described in Group III.

Though there are only six patients in the entire group, the last four have been operated upon since April 1, 1940. After the findings in Group VI had been reviewed (tubular excision of corpus and fundus with gastrojejunostomy—leaving the antrum intact), it became apparent that the performance of a few Finsterer antral exclusion operations accompanied by extensive resection of the acid secreting area, for duodenal ulcer presenting satisfactory indications for operation, would shed additional enlightenment upon the validity of the Edkins' hypothesis in man. As remarked above, under the discussion in Group III, the time element plays an important rôle in making patients achlorhydric after histamine. The first two patients operated upon in this group are achlorhydric to single doses of histamine. The antral exclusion operation is illustrated, together with the other operative procedures, in Figure 4.

**GROUP V—THE SCHMILINSKY OPERATION (PROVISION FOR COMPLETE INTRA-GASTRIC REGURGITATION FOR GASTROJEJUNAL ULCER DEVELOPING AFTER ANTRAL EXCISION)**

Three patients have been operated upon according to this plan of operation. The first patient in the group, operated upon now more than four years ago, has done fairly well. It is to be noted that his emptying time with barium is still extraordinarily slow and he has not been consistently achlorhydric to histamine. Symptomatically, he does quite well. He has been referred to already as Case 1 in Group II.

The experience with the other two patients in this group suggests that the operation should never be performed. Neither patient became achlorhydric, and in both instances the termination was disastrous. In Case 2, perforation of an acute gastrojejunal ulcer in the new efferent loop caused death in a few hours—the perforation occurring four months after performance of the Schmilinsky operation. The old gastrojejunal ulcer healed (ref. footnote, Table V). The other patient developed a large, shallow gastric ulcer which involved a good portion of the residual stomach, and died of uncontrollable gastric hemorrhage, 52 days after performance of the Schmilinsky operation. The old gastrojejunal ulcer healed. The effect of this operative procedure upon the gastric secretory mechanism will be discussed again below under the heading of "Intragastric Regurgitation."

**GROUP VI—TUBULAR EXCISION OF CORPUS AND FUNDUS WITH GASTROJEJUNOSTOMY (LEAVING THE ANTRUM AND PYLORUS INTACT)**

This operation, in principle, is the same as that of the Connell fundusectomy, save that a much larger area of the acid secreting area is excised and with the addition of provision for partial intragastric regurgitation of duodenal content by a coincident gastrojejunostomy. There are five patients in this group. All had duodenal ulcer, and two of the group had both duodenal

and gastric ulcer (Cases 3 and 4). All are now achlorhydric to histamine.\* Several are achlorhydric to triple doses of histamine given subcutaneously. It is to be noted, again, that in two patients in this group (Cases 2 and 5) the lapse of time played an important factor in establishing achlorhydria to histamine stimulation. It should be noted further that the emptying time in this group of patients was not as rapid as in the patients having extensive gastric resection after the Billroth II pattern of operation with terminolateral anasto-

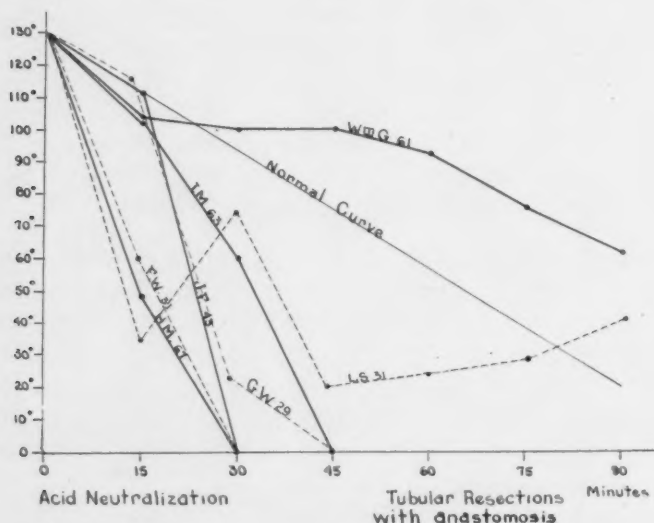


FIG. 5.—Gastric evacuation time after tubular resection with gastrojejunostomy, as indicated by the acid neutralization test.

mosis with the jejunum. No entero-anastomoses were made in this group. The amount of gastric tissue excised, paralleled closely that removed in the extensive gastric resections of Groups III and IV. All are symptomatically well. Roentgenologic examination fails to disclose any evidence of active ulcers. In no instance was the ulcer removed. Roentgenographically, distortion of the duodenal cap as a result of scarring is still present.

#### GROUP VII—TUBULAR EXCISION OF CORPUS AND FUNDUS WITHOUT GASTROJEJUNOSTOMY (LEAVING THE ANTRUM AND PYLORUS INTACT)

Only three patients have been operated upon by this plan. All three were young men with chronic duodenal ulcer causing severe pain and great disability. Massive hemorrhage had not occurred in any of the three cases. None have been achlorhydric, consistently, fasting or after histamine, though one patient was found to be achlorhydric on one occasion to histamine after operation. Significantly, the largest excisions of gastric tissue in the series have been in this group, but without producing achlorhydria. The emptying time in all three patients of this group is rapid. All are symptomatically well.

\* Case 5 was not achlorhydric at the time of the most recent examination.

## PRE- AND POSTOPERATIVE GASTRIC ACIDITY

TABLE VI

PATIENTS HAVING TUBULAR EXCISION OF CORPUS AND FUNDUS WITH GASTROJEJUNOSTOMY

*Leaving the Antrum and Pylorus Intact—No Entero-anastomosis*

Name	Amount Resected (in sq. cm.)	Date of Analysis	Fasting Free Acid	Maximum Free with Histamine	Maximum Total with Histamine	Volume of Secretion ½ hr. (in Cc.)	Acid Output (Histamine) Mg. ½ hr.		Acid Neutralize. % Acid Loss	Motility Emptying Time —Ba.
							Free	Total		
(1)										
Mr. I. M.		3/2/39	12							
677903		3/12/39	12							190 min.
63—D.U.										
3/24/39	180	3/23/39	22							
		3/24/39	28							
		4/3/39	0	10	22	7.0	2.5	5.6		
		5/18/39	0	20	30					
		8/17/39		16	28					
		2/13/40	0	0	32.5	4.7	0	5.0		
		4/18/40	0	0	17					
(2)										
Mr. R. S.		4/18/39	33	62	74	18.0	22.0	49.0		
658862		4/29/39	0	15	30	10.0	5.4	10.9		
31—D.U.		8/29/39	0	0	14	15.0	0	7.7		
4/19/39	263	11/14/39	0	0	48	3.0	0	5.0		
		2/6/40	0	0	48	3.1	0	5.3		
(3)										
Mr. J. F.		11/4/37	0	36	40					
663579		3/28/39	0	30	42					
43—G.U.		5/1/39	0	0	24	5.0	0	4.4		30 min.
4/20/39	244	2/20/40	0	0	30	2.0	0	2.18		40 min.
		3/8/40	0						96	
		4/16/40	0	0*	8*	3.8	0	1.0		
(4)										
Mr. H. M.		5/10/39	35	54	68	24.0	47	60.0		
672813		5/17/39	0	0	14	6.0	0	3.0		
67—G.U.† and D.U.										
5/11/39	262									
(5)										
Mr. W. G.		9/5/39	41							
677176		9/14/39	0	108	116	11.0	42	46.0		
61—D.U.		9/29/39	24	30	60	18.0	19.8	39.4	86	
9/19/39	245	10/5/39	22	42	64	16.3	25	38.0	32	
		3/11/40	0	0	30	5.5	0	6.0		70 min.
		4/24/40	60	76*	116*	2.6	7.2	10.9		

\* Specimens taken 30 minutes after three successive injections of 0.5 mg. of histamine.

† Gastric ulcer at the esophagogastric juncture on the lesser curvature—benign on biopsy.

In Case 1 of this group, the left vagus nerve was cut beside the subdiaphragmatic esophagus. In Case 2, both the vagi were divided below the diaphragm but without any special effect upon gastric secretion.

In young persons, in their twenties, who have chronic duodenal ulcer and present good indications for operation, without a history of massive hemorrhage, this operation has its best indication. Until it is demonstrated definitely



TABLE VII

PATIENTS HAVING TUBULAR EXCISION OF CORPUS AND FUNDUS WITHOUT ANASTOMOSIS

*Leaving the Antrum and Pylorus Intact*

Name	Amount Resected	Date of Analysis	Fasting Free Acid	Maximum Free with Histamine	Maximum Total with Histamine	Volume of Secretion ½ hr. (in Cc.)	Acid Output (Histamine) Mg. ½ hr.		Acid Neutralize. % Acid Loss	Motility Emptying Time —Ba.
Hosp. No.	(in sq. cm.)						Free	Total		
(1)										
Mr. F. W.		12/27/37	63							
664758		3/3/39	88	135	143	49.0	244.0	261		
31—D.U.		10/4/39	70						34	
10/9/39	270	10/6/39	82	114	130	62.0	257.0	293	7	
		10/21/39	0	20	38	46.0	33.0	63	96	
		10/24/39	0							
		11/1/39	—	49	86	14.0	25.0	43	89	8 min.
		12/8/39	0	60	90	17.0	37.2	55	85	
		4/10/40	58	92	106	14.0	47.2	54		
(2)										
Mr. L. S.		1/17/40	34	76	94	19.0	55.0	65	42	
688933		1/30/40	0	10	28	25.0	4.5	25	78	
31—D.U.		3/5/40	26	34	52	19.0	23.5	36	62	6 min.
1/18/40	299	4/23/40	7.5	60	100	9.5	20.8	34.6		25 min.
(3)										
Mr. W. G.		2/6/40	64	74	88	26.0	68.0	83	77	
691263		2/26/40	0	30	74	24.0	26.0	64		70 min.
29—D.U.		4/9/40	0	0	24	4.5	0	4		
2/23/40	359									

that extensive gastric resection performed according to the Billroth II method will insure achlorhydria with regularity, under all circumstances, an operative procedure of this kind will have its place.

*Comment.*—A few facts in this study stand out prominently:

(1) Extensive gastric resection *per se* does not produce achlorhydria to maximal stimulation (histamine), even when combined with bilateral sub-diaphragmatic vagotomy (Group VII).

(2) Extensive gastric resection, when combined with gastrojejunostomy providing opportunity for partial intragastric regurgitation of duodenal content, will produce achlorhydria to maximal stimulation (histamine) usually. The lapse of time is an important factor in the development of such achlorhydria.

(3) Excision of the antrum and pylorus (the small or partial gastric resection) fails to make the residual gastric segment achlorhydric to maximal stimulation.

(4) Allowing the antrum and pylorus to remain, as is indicated particularly by the cases in Group VI, does not militate against securing an achlorhydric stomach to maximal (histamine) stimulation, granted that an extensive gastric resection of the acid secreting area is performed. The cases in Group IV will, with the lapse of more time, shed additional light upon this important issue.

(5) Gastrojejunostomy is not accompanied by achlorhydria to maximal stimulation.

(6) The emptying time is decreased considerably in: (a) All anastomotic operations upon the stomach, Groups I, II, III and IV; (b) after extensive resection of the stomach without anastomosis (Group VII). When the intra-gastric regurgitation of the duodenal content is complete, as it is in Group V, the emptying time is prolonged (barium evacuation time).

*The Size of the Gastric Resection.*—The size of the gastric segment excised has been measured carefully in all patients submitted to operation during the past year. After excision, the surgical pathologist\* tacks the opened specimen on a board under a very slight stretch, which fails to straighten out the rugae of the mucosa and determines the square area, in centimeters, of the excised specimen. This measurement, to be certain, is considerably less than the true area of gastric mucosa removed, into which reckoning account must be taken of the area of the multiple gastric rugae.

In the antral excision series (Group II), the area of the excised gastric tissue varied between 110 and 143 sq. cm., measured as described above—the average for the group was 124 sq. cm. In Group III, in those instances in which the area of the excised tissue was determined, this measurement varied between 178 and 295 sq. cm., the average being 243 sq. cm. For Group IV, the area of the excised gastric tissue varied between 224 and 301 sq. cm., the average being 250 sq. cm. In Group VI, the amount of excised tissue averaged 283 sq. cm. In the successive cases in the group, the respective areas of the excised gastric tissue measured 180, 263, 244, 262 and 244 sq. cm. In the three cases in Group VII, the excised gastric tissue varied between 270 and 359 sq. cm.—averaging 309 sq. cm.

A survey of the data in these groups suggests that excision of 200 sq. cm., or more, of tissue, from the corporic and fundic zones of the stomach of average size, when combined with gastrojejunostomy, after a lapse of time of three to six months after performance of the operation, usually results in an achlor-hydric residual gastric pouch to histamine (0.5 mg.). Some remain achlor-hydric after the triple dose described above. By dividing the gastric tissue, under scrutiny, into squares and triangles, as illustrated in Figure 6, the surgeon may readily determine, in an approximate manner, the extent of the area to be removed. The senior author, who has performed the gastric resections reported here on man, has found that by employing the scheme depicted in Figure 6, he may excise the desired amount of gastric tissue within a margin of error usually not exceeding 5 to 10 per cent. The errors of measurement, with the stomach *in situ*, but devascularized for resection and anastomosis, are usually those of underestimation—that is, the excised specimen, when opened up and tacked down as described above, exhibits an area exceeding that determined at operation by 10 to 20 sq. cm.

In deciding upon the necessary extent of the excision, the surgeon must, of course, be guided by the relative size of the stomach. When the stomach is large and dilated, it is necessary to remove a correspondingly larger segment

\* The writers gratefully acknowledge the helpful interest of Doctor Hebbel, Instructor in Pathology, in many new phases of the problem.

than 200 sq. cm.—which measurement may be suggested as the *minimal* amount to be removed, to secure achlorhydria in the stomach of average size. The senior author has the impression that duodenal ulcers are more likely to have large stomachs than gastric ulcers (excluding, of course, the pyloric ulcer). An ulcer on the lesser curvature causes shortening, frequently with a resultant smaller stomach. Duodenal ulcer, on the contrary, is more likely to be attended by obstruction and gastric enlargement.

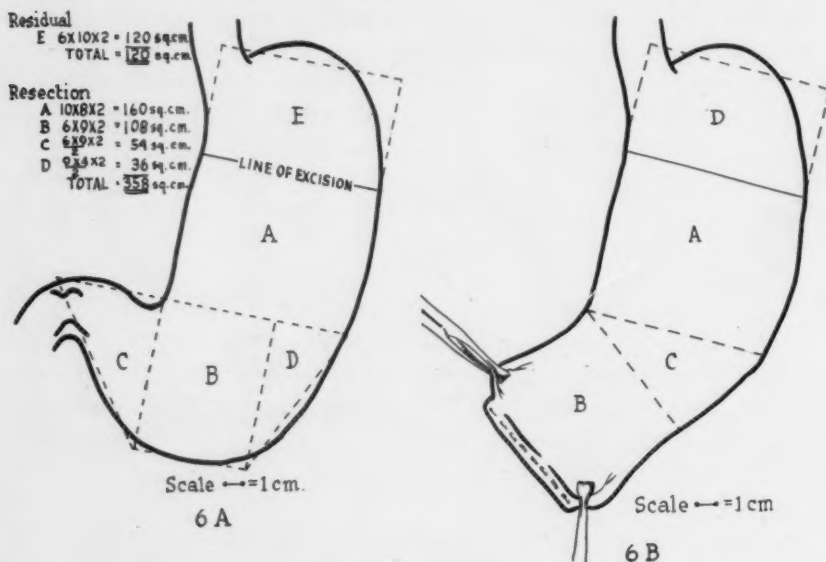


FIG. 6.—Proposed scheme for determining the surface area of the stomach at operation. It may be done as indicated in 6 A or 6 B, or by some variant thereof.

In order to procure achlorhydria with a high degree of regularity, it is necessary to sacrifice 66 to 80 per cent of the gastric tissue. In the literature, one hears much of small (partial) and extensive (subtotal) resections. Finsterer (1923), who has been an ardent advocate of extensive excision, has insisted the line of division of the stomach should be vertical to the axis of the body. We have enlarged Finsterer's illustration of the proposed segment for removal three times, employing small cardboard plaques cut to pattern, and have weighed these out on a fine balance scale. Figure 7 indicates the per cent of the total gastric tissue removed by Finsterer's plan (52 per cent) and confirms the impression, that in allowing so great a length of the greater curvature to remain, it is not likely that the surgeon can excise two-thirds to three-fourths of the stomach. In the diagram, indicating the manner in which the gastric tissue is triangulated and squared-off for excision, is illustrated also the usual extent of the excision as well as the usual size of the residual segment. This type of resection, when accompanied by gastrojejunostomy, is, in the course of a few months, likely to be accompanied by achlorhydria even to histamine stimulation. We have no case with total anacidity. In Case 5

in Group III, at least 95 per cent of the stomach was removed, the lesion being at the esophagogastric juncture on the lesser curvature. The lesion which was believed to be carcinoma proved to be benign. Unfortunately only one preoperative gastric analysis was made.

*The Rôle of the Stoma in the Production of Achlorhydria.*—From inspection of the tables it is apparent that extensive gastric resection *per se* cannot produce achlorhydria, nor can gastrojejunostomy alone. A number of years ago, Harvey (1907) examined the gastric mucous membrane in the vicinity of gastro-enterostomy stomata in dogs, some months after performance of the operation. He observed disappearance of parietal cells from the gastric tubules—cells responsible for the secretion of hydrochloric acid. Since gas-

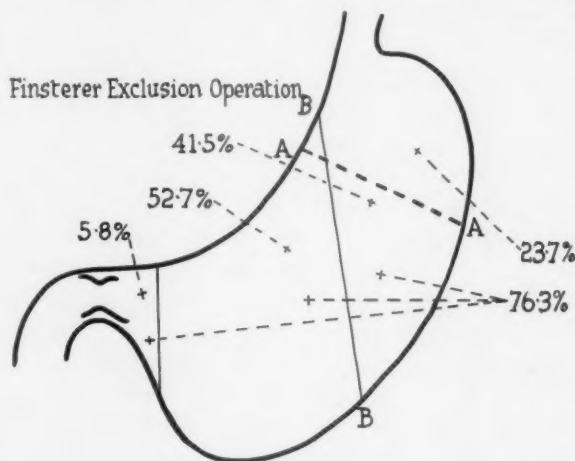


FIG. 7.—Finsterer's (1923) "subtotal" gastric resection with pyloric exclusion. The actual area removed is 52.7 per cent of the total. By elevating the line of excision on the greater curvature to a higher level, more than 70 per cent of the stomach may be removed.

trosopy has come into quite general use, atrophy and edema of the mucous membrane are not uncommon endoscopic observations upon the operated stomach. Of the present series, the larger number have been subjected to gastroscopic examination. Those findings, however, must await further analysis.

Inasmuch as the time factor appears to be an important item in the establishment of achlorhydria following extensive gastric resection and gastrojejunostomy, it is not unlikely that regurgitated duodenal contents impair the capacity of the parietal cells to secrete hydrochloric acid.

The relatively high total acidities, exhibited by some cases in Tables III and VI, free hydrochloric acid being absent, suggest that hydrochloric acid is either being secreted at a slower rate (most likely) or that with the establishment of the gastrojejunal stoma, more mucus is, through one agency or another (gastric, biliary, duodenal and jejunal), made available to combine with the free acid. It is not unlikely, when ulcer occurs spontaneously in man or is produced experimentally in the cat by intragastric instillation of

acid or the subcutaneous implantation of histamine (see below), that the rapid flow of hydrochloric acid (or secretion as a result of histamine stimulation) over the gastric mucosa washes mucus, the normal buffer for acid, away. When the rate of secretion of hydrochloric acid is slowed up by extensive gastric resection and gastrojejunostomy, enough mucus becomes available to neutralize hydrochloric acid as it is secreted by the gastric glands.

The mechanism by which achlorhydria occurs following excision of gastric tissue and the establishment of gastrojejunostomy, it must be said, is not wholly clear. It is not unlikely that it may be found to be a problem in colloid adsorption chemistry. The manner of adsorption of acid by protein (mucus) in the presence of bile and pancreatic juice on gastric and jejunal mucosal surfaces may have to be studied to solve the problem.

With the cooperation of Dr. Wallace D. Armstrong, associate professor of physiological chemistry, at the University of Minnesota, we recently undertook verification of the values titrated as total acid as being largely hydrochloric acid combined with protein, in patients and dogs in whose gastric contents, after extensive gastric resection and gastrojejunostomy no free hydrochloric acid was found. Much to our surprise, we found considerably less acid in these gastric contents than our titration figures for total acidity (in the absence of free HCl) had suggested. In explanation of this occurrence, Doctor Armstrong says: "The combined acid of gastric juice as determined by the difference between the results of analysis for free acid and total acid has usually been considered to represent, in greatest part, hydrochloric acid combined with protein. It appears very probable that the combined acid should not be interpreted to indicate only hydrochloric acid combined with protein, but also, in addition, the base combining ability of the protein. Proteins, on the alkaline side of their isoelectric point, possess the ability to act as an acid and so combine with base. In general, the base combining power of a protein increases as the  $p_H$  of the medium is raised above the isoelectric point of the protein. Since the end-point of the titration of total acid has arbitrarily been fixed at the  $p_H$  required to color phenolphthalein ( $p_H$  8.3), it seems certain that a good deal of the alkali used in the titration of total acid is really used in the neutralization of the base combining groups of the protein of the fluid. Thus, the determined value for combined acid represents the alkali required to neutralize the hydrochloric acid combined with proteins plus that needed to neutralize the buffering ability of the protein. The relative proportions of the two will be expected to vary with circumstances depending upon the total hydrochloric acid and protein contents of the fluid."

In this connection, it may not be amiss to discuss briefly the commonly expressed belief that a gastric ulcer becomes achlorhydric more readily after the same type of operative procedure than does duodenal ulcer (Perman, 1935, and Walters, 1937). It is known also that patients with duodenal ulcer tend, in the main, to have higher acid values than gastric ulcer. This may in part be a matter of the size of the stomach as suggested above. However, a gastric ulcer in its typical location, on the mid lesser curvature, with



the frequent attendant indurative edema, radiating several centimeters in each direction into the acid secreting area of the stomach, is likely to injure somewhat the capacity of the stomach to secrete hydrochloric acid.

*The Amount of Intragastric Regurgitation.*—In this connection, the Schmilinsky operation affords an opportunity to evaluate the effect of total intragastric regurgitation of the duodenal content. Up until now, the beneficial effects of intragastric regurgitation accompanying anastomotic types of operation, such as gastrojejunostomy, have been attributed to neutralization and dilution of the acid secretions of the stomach. From the few experiences reported here with the Schmilinsky procedure, it is apparent that it is a highly undesirable type of operation. In this connection, it is to be remembered that McCann reported, in 1929, the development of ulcers at the new gastric outlet in 80 per cent of a series of 26 dogs, when the total duodenal secretions were drained back into the gastric fundus. Ivy and Fauley (1931), Weiss, Graves and Gurriaran (1932), and Graves (1935) repeated the McCann experiment, draining the duodenal secretions back, however, into the gastric antrum instead of into the fundus as McCann did. Except for Ivy and Fauley, who noted the occurrence of gastrojejunal ulcers twice at the new gastric outlet, no ulcers were obtained by the other observers. Maier and Grossman (1937) repeated the McCann experiment very much in the manner that McCann performed it initially, but only two dogs out of 12 developed gastrojejunal ulcers. We, too, have eight dogs with the McCann application of the Schmilinsky procedure; in four animals the duodenal content was drained back into the fundus, and in the remaining four into the antrum. All appear well. Four (two of each) have been reexplored after the lapse of at least four months' time in each instance, but no ulcers have been observed. Still our meager but unfortunate experience with the Schmilinsky procedure confirms McCann's observations and stamps total intragastric regurgitation of the duodenal contents as undesirable. An additional dog has been kept under observation in the experimental laboratory for more than a year, with the Schmilinsky operation performed as illustrated in Figure 4 (Group V). The pylorus and antrum have been removed and the dog is not achlorhydric despite total intragastric regurgitation of the duodenal content (ref. Table VIII).

What may be the explanation of this unusual behavior? To the senior author, only one explanation appears plausible, namely, provision for complete intragastric regurgitation protracts, interminably, the second phase (gastric) of gastric secretion and probably intensifies the intestinal phase as well. That is, the acid secreting cells in the residual gastric pouch are constantly stimulated. In time, with the lapse of years, as in Case 1 in Groups II and V, a relative achlorhydria may occur, ultimately, granted that the sequelae of gastric autolysis or perforation of a new gastrojejunal ulcer does not occur in the meanwhile.

*The Size of the Stoma and the Question of Entero-anastomosis.*—The ideal length of the gastrojejunal stoma is not known. In the earlier group

of cases, operated upon after the Billroth II plan of operation, a complete terminolateral (Pólya) anastomosis was made. Latterly, an incomplete (inferior) terminolateral (Hofmeister) anastomosis 5 cm. in length has been made. In a number of these an entero-anastomosis has been made also. The results of the Schmilinsky procedure suggest, quite definitely, that complete intragastric regurgitation is an undesirable feature. In the main, the large stomata (complete terminolateral anastomosis) empty unusually rapidly ("dumping stomachs"). Whether there is more or less intragastric regurgitation with a large or small stoma is difficult to ascertain definitely.

TABLE VIII

GASTRIC ACIDITY IN DOG'S STOMACH AFTER ESTABLISHMENT OF COMPLETE INTRAGASTRIC REGURGITATION OF DUODENAL CONTENT INTO THE FUNDUS

*Schmilinsky Operation*

Dog No. 3—Blackie:

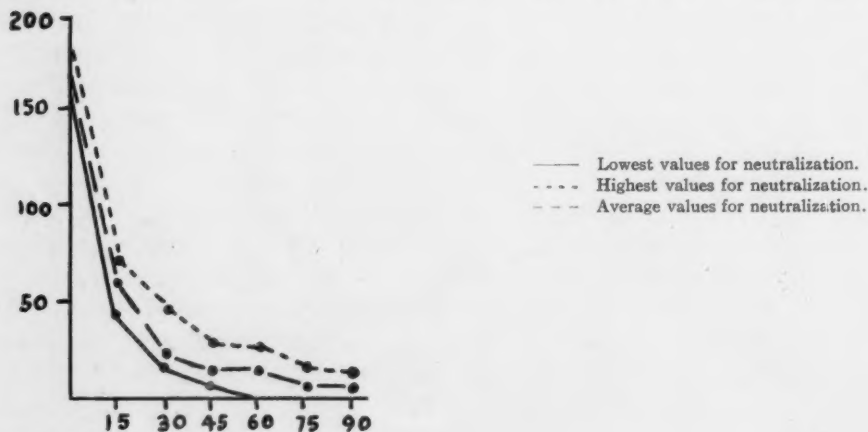
*Procedures and Dates*

Antral resection 3/20/39

Duodenogastrostomy 5/17/39

(Schmilinsky)

Dates of Analysis	Fasting Free Acid	Alcohol Free Acid	Histamine Free Acid			Histamine Total Acid			Milligrams HCl with Histamine (Average)	
			Max.	Av.	Min.	Max.	Av.	Min.	Free	Total
4/11/39.....	0	12		73			88		113.4	138.0
4/12/39.....	0	11		24			104		17.6	76.0
4/13/39.....	0	23		24			48		12.2	24.4
4/24/39.....	0	25.5		34			58		17.45	12.8
2/14/40.....	0	0	62	32	0	86	62	50	31.5	60.4
2/15/40.....	0	0	14	4	0	57	46	40	5.6	18.6
4/25/40.....	0	12	56	37	0	64	44	10	26.8	32.3



Dr. George S. Bergh, of this department, and Drs. Curtis Nessa and Solveig Bergh, of the Department of Roentgenology, have studied intragastric

regurgitation occurring through gastrojejunostomy stomata by injecting barium and phenolsulphonphthalein in small amounts through a duodenal tube, the tip of which lies well into the duodenum. The amounts of intragastric regurgitation are variable. In the main, regurgitation to the extent of 33 per cent is common in the supine position—a figure which is considerably larger than when the patient stands erect.

In the antral excisions (Group II—six cases) a complete terminolateral anastomosis was made in all instances; achlorhydria to histamine (maximal) stimulation in this group was rare. In the extensive resections (Group III—ten cases) a complete terminolateral anastomosis was made in six patients and an entero-anastomosis was made also six times; in four of the patients with incomplete terminolateral anastomosis and in two of the others. In the antral exclusions (Group IV—six cases) complete terminolateral anastomosis was made only twice and an entero-anastomosis was made in five instances. In the tubular resections (Group VI—five cases) no entero-anastomoses were made.

It is difficult to draw any pertinent conclusions from the gastric acidities exhibited by these variants in the operative procedure. Yet, it does appear that an entero-anastomosis, if small (3.5 to 4 cm. in length) and placed near the gastrojejunal stoma, may be a helpful procedure, in that, while permitting intragastric regurgitation, it prevents undue prolongation of the gastric phase of gastric secretion by reducing the amount of the duodenal content regurgitated into the stomach. It seems worth while to determine the validity of this premise. It is to be understood clearly, however, that these latter remarks have *no meaning* for any other operation than extensive gastric resection, of the extent herein described.

*Gastrojejunal Ulcer.*—Bergh, Hay and Trach found in studying 138 patients having gastrojejunostomy, available for examination in the University Out-Patient Clinic, that 14 of the group had gastrojejunal ulcer (10.1 per cent). However, only 100 of the group had their gastrojejunostomy operation performed at the University Hospital; five of these had gastrojejunal ulcer (5 per cent). Yet others in the group may still develop gastrojejunal ulcer. Case 8 in Group III, upon whom emergency operation was performed for massive gastric hemorrhage, developed gastrojejunal ulcer (the cause of the bleeding) 20 years after gastrojejunostomy for obstructive duodenal ulcer.\* In the experience of Church and Hinton (1940), gastrojejunal ulcer is a far more common sequel to gastrojejunostomy than is generally believed.

Two of the six patients in Group II (these patients appear again in Group V, Cases 1 and 2) with excision of antrum and pylorus developed gastrojejunal ulcer (33 per cent). Klein and his associates (1933) have reported previously an incidence of gastrojejunal ulcer following partial gastric resection of 8.5 per cent, and Lahey and Swinton (1935) noted this as a not infrequent complication of partial gastrectomy for ulcer.

\* A patient who developed gastrojejunal ulcer 28 years after gastro-enterostomy was observed recently.

The only other gastrojejunal ulcer in this group of resections is Case 3 in Group V. He came with a gastrojejunal ulcer and when it was excised a portion of the greater curvature was excised, establishing a new gastrojejunostomy stoma in the line of excision. The stomach was extraordinarily large and the excision of 214 sq. cm. of gastric tissue was inadequate to make the patient achlorhydric.

No recurrent ulcers have been observed in any of the other group of patients.

Starlinger (1930) conducted a written inquiry on the incidence of gastrojejunal or recurrent ulcer after various types of gastric resection. Among 25,121 cases, constituting the basis of his report, only 169 patients were reported as having gastrojejunal or recurrent ulcer (0.7 per cent)—certainly a very conservative estimate (an unsatisfactory manner, however, in which to study its incidence).

Finsterer (1934) admits an incidence of gastrojejunal ulcer of 6.1 per cent after his operation of antral exclusion accompanied by gastric resection. As pointed out above, Finsterer, in insisting on a line of division of the stomach parallel to the vertical axis of the body, must of necessity leave more greater curvature than he is warranted in doing, mindful of the importance of extensive excision of gastric tissue to insure achlorhydria.

TABLE IX

## EFFECT OF ANTRAL EXCISION IN STAGES UPON GASTRIC ACIDITY

(Pavlov Pouch and Residual Stomach)

## PREOPERATIVE DETERMINATIONS

Dog No. 92—Johnny

	STOMACH SECRETION		
	No. of Determinations—2		
	Degrees of Free Acid		
	Maximum	Average	Minimum
Fasting—1 hr.:			
Free.....	48	39	29
Total.....	55	47	38
Alcohol—½ hr.:			
Free.....	80	72	64
Total.....	87	79	70
Histamine—½ hr.:			
Free.....	91	89	87
Total.....	101	99	90
Histamine—1 hr.:			
Free.....	109	106	102
Total.....	115	113	110
Histamine—1 ½ hr.:			
Free.....	69	69	69
Total.....	76	76	76

(See insert for continuation of Table IX)





TABLE IX (Continued)  
(A) AFTER ESTABLISHMENT OF PAVLOV POUCH  
Operation, October 2, 1939

	RESIDUAL STOMACH									PAVLOV POUCH								
	No. of Determinations—3									No. of Determinations—12								
	Degrees of Acid			Volume—Cc.			Milligrams HCl			Degrees of Acid			Volume—Cc.			Milligrams HCl		
	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.
Fasting—1 hr.																		
Free.....	0	0	0	2.5	1.4	0.0	0.0	0.0	0.0	20	2	0	4.3	1.6	0.0	3.1	0.1	0.0
Total.....	47	32	16				4.3	1.6	0.0	150	52	0				23.5	3.0	0.0
Veal meal— $\frac{1}{2}$ hr.																		
Free.....										56	8	0	6.6	2.1	0.4	13.5	0.6	0.0
Total.....										93	66	33				22.4	5.0	0.0
Alcohol— $\frac{1}{2}$ hr.																		
Free.....	22	10	0	3.4	2.6	2.0	2.7	1.0	0.0	132	83	0	15.0	9.2	1.9	72.4	31.4	0.0
Total.....	39	36	32				5.0	3.4	2.3	130	114	60				71.2	38.4	0.0
Histamine— $\frac{1}{2}$ hr.																		
Free.....	76	31	0	6.5	3.6	1.7	18.0	4.1	0.0	140	119	76	23.8	14.0	2.7	120.4	61.0	7.5
Total.....	88	56	32				21.0	7.3	2.0	154	139	110				136.7	71.1	10.9
Histamine—1 hr.																		
Free.....	45	34	24	4.5	3.6	2.3	7.4	3.7	2.0	146	130	110	25.0	11.7	1.0	132.9	50.8	4.0
Total.....	76	62	44				12.5	6.9	3.7	168	144	114				153.2	60.2	4.2
Histamine—1 $\frac{1}{2}$ hrs.																		
Free.....	34	11	0	5.3	3.2	1.7	6.6	1.3	0.0	128	75	40	4.3	1.6	0.2	20.0	4.4	0.3
Total.....	60	45	20				11.6	5.3	0.0	172	142	100				27.1	8.3	0.7

(B) AFTER ANTRAL EXCLUSION  
Operation, November 13, 1939

	No. of Determinations—5									No. of Determinations—9								
	Degrees of Acid			Volume—Cc.			Milligrams HCl			Degrees of Acid			Volume—Cc.			Milligrams HCl		
	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.
Fasting—1 hr.																		
Free.....	20	4	0	7.5	5.3	1.0	5.5	0.8	0.0	40	4	0	1.5	0.8	0.4	2.2	1.2	0.0
Total.....	54	33	20				14.3	6.5	0.7	135	110	80				7.4	3.2	1.3
Veal meal— $\frac{1}{2}$ hr.																		
Free.....	0	0	0	4.6	3.7	2.9	0.0	0.0	0.0	0	0	0	0.8	0.3	0.1	0.0	0.0	0.0
Total.....	78	72	68				13.2	8.1	5.4	150	94	50				4.4	1.1	0.2
Alcohol— $\frac{1}{2}$ hr.																		
Free.....	0	0	0	22.8	11.2	2.3	0.0	0.0	0.0	114	76	36	11.1	7.1	2.2	45.9	22.5	2.9
Total.....	72	60	44				58.8	24.2	3.7	134	104	66				54.4	26.9	5.3
Histamine— $\frac{1}{2}$ hr.																		
Free.....	22	13	0	25.0	12.8	6.2	20.0	6.1	0.0	146	134	120	17.0	12.5	8.1	90.2	61.3	35.5
Total.....	66	49	19				60.2	36.9	4.3	162	147	135				100.5	67.6	38.4
Histamine—1 hr.																		
Free.....	20	10	0	24.5	12.7	2.0	17.9	4.6	0.0	150	141	133	17.5	12.6	2.1	86.1	64.9	9.2
Total.....	80	37	15				71.5	17.2	2.0	180	155	144				114.8	70.2	11.0
Histamine—1 $\frac{1}{2}$ hrs.																		
Free.....	0	0	0	17.4	7.2	2.5	0.0	0.0	0.0	135	121	80	6.5	2.4	1.0	32.1	10.6	2.9
Total.....	52	35	15				33.0	8.1	1.4	180	141	106				42.7	12.2	3.9

(C) AFTER ISOLATION OF ANTRAL POUCH  
Operation, January 11, 1940

	RESIDUAL STOMACH									PAVLOV POUCH									ANTRAL POUCH								
	No. of Determinations—2									No. of Determinations—4									No. of Determinations—4								
	Degrees of Acid			Volume—Cc.			Milligrams HCl			Degrees of Acid			Volume—Cc.			Milligrams HCl			Degrees of Acid			Volume—Cc.			Milligrams HCl		
	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.
Fasting—1 hr.																											
Free.....	0	0	0	15.0	8.2	1.4	0.0	0.0	0.0	103	75	30	3.0	1.5	0.4	11.4	4.1	0.4	52	21	0	7.0	2.9	1.2	13.3	2.3	0.0
Total.....	57	53	48				31.3	15.9	2.5	173	109	55				18.9	6.0	0.8	112	59	28				28.8	6.2	1.2
Veal meal—½ hr.																											
Free.....	0	0	0	2.0	2.0	2.0	0.0	0.0	0.0	110	100	90	1.5	1.3	1.0	6.1	4.8	3.3	64	28	0	4.0	2.6	1.4	9.3	1.4	0.0
Total.....	120	120	120				3.8	8.8	8.8	115	108	100				6.4	5.1	3.7	120	83	43				17.5	8.1	2.2
Alcohol—½ hr.																											
Free.....	20	10	0	4.2	3.5	2.7	3.1	1.3	0.0	140	96	52	12.5	8.4	3.0	64.0	29.4	5.7	124	67	0	12.5	7.1	3.0	56.4	17.4	0.0
Total.....	43	42	40				6.7	5.4	4.0	150	118	64				68.7	36.1	7.0	144	101	26				65.4	26.2	2.9
Histamine—½ hr.																											
Free.....	20	17	14	5.5	4.2	2.8	4.0	2.6	1.4	152	142	124	18.5	13.8	11.0	102.8	71.2	50.0	138	117	80	17.5	13.9	11.0	88.2	59.5	32.0
Total.....	32	29	26				6.4	4.4	2.7	160	151	132				107.8	75.8	53.0	154	137	96				98.5	67.2	38.5
Histamine—1 hr.																											
Free.....	40	35	30	11.0	8.3	5.5	16.0	10.7	6.0	150	149	148	21.0	18.1	14.0	114.8	99.3	75.2	164	148	140	28.0	21.5	14.0	168.0	114.9	71.6
Total.....	52	51	50				21.0	15.5	10.0	168	159	154				128.4	105.0	79.0	170	159	152				175.0	124.8	77.6
Histamine—1 ½ hrs.																											
Free.....	32	16	0	4.2	3.7	3.1	4.9	2.1	0.0	150	143	140	11.8	6.3	2.7	64.6	32.5	13.8	136	132	128	16.0	7.7	2.7	78.8	35.0	10.0
Total.....	64	44	23				9.8	6.1	2.5	172	156	140				73.4	36.0	13.8	160	150	144				93.0	84.4	14.1

(D) AFTER EXCISION OF ANTRAL POUCH  
Operation, April 10, 1940

	No. of Determinations—3									No. of Determinations—3								
Fasting—1 hr.																		
Free.....	0	0	0	3.8	2.0	1.6	0.0	0.0	0.0	60	20	0	3.4	1.2	0.1	7.4	0.9	0.0
Total.....	36	28	20				4.9	2.0	1.2	68	59	50				8.4	2.6	0.2
Meat—½ hr.																		
Free.....	0	0	0	7.5	7.5	7.5	0.0	0.0	0.0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0
Total.....	26	26	26				7.1	7.1	7.1									
Alcohol—½ hr.																		
Free.....	0	0	0	11.0	7.4	3.8	0.0	0.0	0.0	112	89	75	5.2	3.4	3.0	21.1	11.1	8.2
Total.....	28	23	18				11.2	6.2	2.5	120	193	90				23.8	12.8	9.9
Histamine—½ hr.																		
Free.....	10	3	0	6.5	5.2	3.8	2.4	1.0	0.0	142	135	128	17.0	15.0	13.0	87.2	74.0	60.8
Total.....	24	21	14				5.7	4.0	1.9	150	141	134				93.1	77.6	63.9
Histamine—1 hr.																		

Total.....	57	53	48	13.0	6.2	1.4	0.0	0.0	0.0	103	75	30	3.0	1.5	0.4	11.4	4.1	0.4	52	21	0	7.0	2.9	1.2	13.3	2.3	0.0
Veal meal—½ hr.																											
Free.....	0	0	0	2.0	2.0	2.0	0.0	0.0	0.0	110	100	90	1.5	1.3	1.0	6.1	4.8	3.3	64	28	0	4.0	2.6	1.4	9.3	1.4	0.0
Total.....	120	120	120				3.8	8.8	8.8	115	108	100				6.4	5.1	3.7	120	83	43				17.5	8.1	2.2
Alcohol—½ hr.																											
Free.....	20	10	0	4.2	3.5	2.7	3.1	1.3	0.0	140	96	52	12.5	8.4	3.0	64.0	29.4	5.7	124	67	0	12.5	7.1	3.0	56.4	17.4	0.0
Total.....	43	42	40				6.7	5.4	4.0	150	118	64				68.7	36.1	7.0	144	101	26				65.4	26.2	2.9
Histamine—½ hr.																											
Free.....	20	17	14	5.5	4.2	2.8	4.0	2.6	1.4	152	142	124	18.5	13.8	11.0	102.8	71.2	50.0	138	117	80	17.5	13.9	11.0	88.2	59.5	32.0
Total.....	32	29	26				6.4	4.4	2.7	160	151	132				107.8	75.8	53.0	154	137	96				98.5	67.2	38.5
Histamine—1 hr.																											
Free.....	40	35	30	11.0	8.3	5.5	16.0	10.7	6.0	150	149	148	21.0	18.1	14.0	114.8	99.3	75.2	164	148	140	28.0	21.5	14.0	168.0	114.9	71.6
Total.....	52	51	50				21.0	15.5	10.0	168	159	154				128.4	105.0	79.0	170	159	152				175.0	124.8	77.6
Histamine—1 ½ hrs.																											
Free.....	32	16	0	4.2	3.7	3.1	4.9	2.1	0.0	150	143	140	11.8	6.3	2.7	64.6	32.5	13.8	136	132	128	16.0	7.7	2.7	78.8	35.0	10.0
Total.....	64	44	23				9.8	6.1	2.5	172	156	140				73.4	36.0	13.8	160	150	144				93.0	84.4	14.1

(D) AFTER EXCISION OF ANTRAL POUCH

Operation, April 10, 1940

	No. of Determinations—3									No. of Determinations—3								
Fasting—1 hr.																		
Free.....	0	0	0	3.8	2.0	1.6	0.0	0.0	0.0	60	20	0	3.4	1.2	0.1	7.4	0.9	0.0
Total.....	36	28	20				4.9	2.0	1.2	68	59	50				8.4	2.6	0.2
Meat—½ hr.																		
Free.....	0	0	0	7.5	7.5	7.5	0.0	0.0	0.0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0
Total.....	26	26	26				7.1	7.1	7.1									
Alcohol—½ hr.																		
Free.....	0	0	0	11.0	7.4	3.8	0.0	0.0	0.0	112	89	75	5.2	3.4	3.0	21.1	11.1	8.2
Total.....	28	23	18				11.2	6.2	2.5	120	193	90				23.8	12.8	9.9
Histamine—½ hr.																		
Free.....	10	3	0	6.5	5.2	3.8	2.4	1.0	0.0	142	135	128	17.0	15.0	13.0	87.2	74.0	60.8
Total.....	24	21	14				5.7	4.0	1.9	150	141	134				93.1	77.6	63.9
Histamine—1 hr.																		
Free.....	0	0	0	7.9	5.3	2.9	0.0	0.0	0.0	146	146	146	12.0	10.4	8.8	58.7	55.3	46.6
Total.....	32	23	14				8.2	4.5	1.5	152	151	150				66.8	54.0	48.0
Histamine—1 ½ hrs.																		
Free.....	0	0	0	12.0	9.2	6.1	0.0	0.0	0.0	157	135	100	1.6	1.0	0.7	9.3	4.9	2.6
Total.....	20	16	10				8.8	5.4	2.2	171	152	133				10.0	5.5	3.4







Balfour (1928) relates that 26 per cent of gastrojejunal ulcers coming under his observation have achlorhydria. It is very unlikely, however, that any patient with a well authenticated ulcer or gastrojejunal ulcer has a true achlorhydria—that is, is persistently achlorhydric after maximal stimulation with histamine. We have seen no such cases.

The absence of ulcer in patients with pernicious anemia (Kahn, 1937) having achlorhydria, and the absence of stomach ulcers in patients having gastric resection with gastrojejunostomy for cancer, bespeak the importance of acid in the genesis of ulcer, as does also the occurrence of an ulcer in Meckel's diverticulum where only a small fragment of gastric mucosa may cause ulceration with perforation or severe hemorrhage.

Among those who employ gastrojejunostomy for ulcer, the first and most positive indication for the operation is duodenal ulcer with obstruction. In this connection, the experience of those who have practiced the Eiselberg operation of gastrojejunostomy with pyloric exclusion is most important. It is generally conceded that the incidence of gastrojejunal ulcer after the Eiselberg operation is approximately 25 per cent. Only reopening of the pylorus when gastrojejunostomy is undertaken for obstructive ulcer can save the patient from running a similar risk of this dreaded complication. Moreover, Dublin and his associates, of the Metropolitan Life Insurance Company, in speaking of the risks of patients with ulcer, state that recurrent ulcer is the most important factor in mortality of patients who have been operated upon for ulcer.

Graham and Lewis (1935) state that they performed the Devine exclusion operation (transverse division of the stomach at the incisura without excision of gastric tissue) five times, and gastrojejunal ulcer developed at the stoma in all five patients.

*Night Secretion.*—Pavlov believed that fasting was attended by absence of gastric secretion in the dog. Carlson (1916) showed quite definitely, however, for man that the secretion of hydrochloric acid was continuous, and observers since (Polland and Bloomfield) have come to speak of a basal secretion of hydrochloric acid. Winkelstein believed that secretion of free hydrochloric acid at night occurred only in patients with ulcer and was absent in patients with a normal gastric secretory response without ulcer.

Our findings (Mears and Hay) on this score confirm the previous observations of Carlson, Polland and Bloomfield, and Hellebrandt, Tepper, Grant and Catherwood. In the main, however, patients with ulcer secrete more hydrochloric acid at night than do patients with normal stomachs. Undoubtedly, this item of night secretion, which will receive but bare mention here, is an important element in the dietary control of ulcer, and probably one of the most important items causing failure of such management. If some manner of suppressing night secretion adequately or controlling it continuously could be evolved, the necessity for surgery in the management of ulcer would diminish considerably. Measures such as suggested by Sand-

weiss (1939) and Brunschwig and his associates (1940) may, some day, make the rôle of the surgeon less prominent in dealing with the ulcer problem.

During the time that the work described above has been under way in the clinic, a broad approach to the ulcer problem has been made in the laboratory. Only a few observations, bearing somewhat intimately upon the questions described above, will be recited here.

*Pouch Experiments in the Dog and the Edkins Hypothesis.*—The validity of the Edkins' hypothesis was put to experimental test in the dog, employing methods very similar to those described previously by Smidt, Portis and Portis, Priestley and Mann, Enderlen and Zukschwerdt, and Shapiro and Berg.

*Method.*—A preliminary assay of the gastric secretory response was first made on the intact stomach. Then, either a Pavlov or a Heidenhain pouch was made of the proximal half of the greater curvature of the stomach and

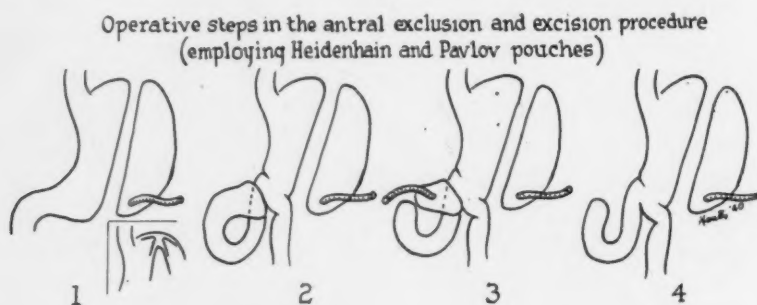


FIG. 8.—The various operative steps carried out in trying to evaluate the Edkins hypothesis experimentally by antral excision:

1. Establishment of a Heidenhain or Pavlov pouch.
2. Antral exclusion—the line of division being made in the acid secreting area of the stomach.
3. Isolation of the antral pouch.
4. After excision of the antral pouch.

the fundus. After complete recovery of the animal, the gastric response in both the residual stomach and the pouch was determined again. Later, an antral exclusion operation was performed, dividing the stomach transversely, the site of section being at or slightly above the incisura. The upper segment of the stomach was then anastomosed to a loop of jejunum. Determinations were made of the gastric secretory response in (1) the residual stomach; (2) the antral pouch; and (3) the Pavlov or Heidenhain pouch. Finally, the antral pouch was excised and the effect of its excision noted upon the gastric secretory response in the residual stomach and the Heidenhain or Pavlov pouch.

A number of such experiments have been completed. Excision of the antral pouch has been completed only recently in the majority. Nevertheless, our experiments indicate quite definitely that excision of the antrum and pylorus has no effect upon the secretory response in Pavlov or Heidenhain pouches in the fundus.



Portis and Portis, and Shapiro and Berg, while noting the absence of effect of antral excision upon the behavior of Pavlov pouches in the fundus of the dog's stomach, described also complete achlorhydria in the residual gastric segment (Portis and Portis), or a distinct lowering of acidity in the residual gastric segment (Shapiro and Berg). However, no special significance was attributed to this occurrence. Yet this is a *most* significant item. Our experiments still fail to indicate whether this is a regurgitation phenomenon (impaired function of acid secreting cells in response to intra-gastric regurgitation of duodenal contents as consequence of gastric resection and gastrojejunostomy) or whether sacrifice of the antrum and pylorus reduces the ability of the residual gastric pouch to sustain the initial capacity for secretion of hydrochloric acid. Reasoning by analogy, having in mind the absence of effect of antral excision upon the secretory capacity of Pavlov or Heidenhain pouches (also see Table X), one might say logically, it must be the regurgitation factor. Factual information can be obtained on this point in the dog which will eliminate the potential errors of apparently sound logic.

Summarizing data are given in Table IX on one such dog after: (1) Establishment of a Pavlov pouch; (2) antral exclusion; (3) isolation of

TABLE X

GASTRIC ACIDITY IN LARGE GASTRIC POUCH AND IN SMALL RESIDUAL STOMACH (AFTER GASTRO-JEJUNOSTOMY) FOLLOWING ESTABLISHMENT OF SUBTOTAL GASTRIC POUCH

Dog No. 9—Tony:

Procedures and Dates

Subtotal gastric pouch 5/26/39

Residual stomach approx. 20%

Residual Stomach						Subtotal Pouch					
Degrees			Mg. HCl in			Degrees			Mg. HCl in		
Free Acid	Total Acid	Volume Cc.	Free Acid	Total Acid		Free Acid	Total Acid	Volume Cc.	Free Acid	Total Acid	
<b>5/12/39</b>											
Preoperative											
Determinations:											
Fasting—1 hr.	24	46									
Veal broth—1 hr.	25	48									
Alcohol—½ hr.	66	80									
Histamine—½ hr.	76	90									
Histamine—1 hr.	16	32									
Histamine—1½ hr.	15	33									
<b>3/1/40</b>											
Postoperative											
Determinations*											
Fasting—1 hr.	0	36	2.7	0	3.55	40	72	3.5	5.08	9.13	
Veal meal—½ hr.	0	56	14	0	28.6	132	146	13	63.0	69.0	
Alcohol—½ hr.	0	28	10	0	10.2	146	158	15	79.6	86.5	
Histamine—½ hr.	0	60	17	0	37.2	144	156	13	68.0	74.2	
Histamine—1 hr.	0	60	20	0	43.8	152	164	12	66.8	72.0	
Histamine—1½ hr.	0	48	9	0	15.8	152	162	14	77.6	82.8	

\* In three subsequent determinations the residual stomach was achlorhydric to these stimuli. Achlorhydria in the residual gastric pouch on histamine stimulation since 8/31/39.

antrum as a pouch; and (4) excision of antral pouch and pylorus. Our antral pouches, as we had anticipated, contained, quite uniformly, a fragment of the acid secreting area on the upper end. We wanted to be certain, when the antral pouch was removed, that no antral mucosa remained. The secretion from these antral pouches was, therefore, acid in reaction.

In another dog with a subtotal gastric pouch (isolation of entire stomach save for a small remnant of the fundus), a jejunofundic anastomosis was made. It is to be observed (Table X) that the isolated stomach secretes hydrochloric acid actively. The small residual stomach between esophagus and jejunum, however, has, with the lapse of time, become achlorhydric.



FIG. 9.—Drawing of ulcers produced by subcutaneous implantation of histamine in cat.

*Acid Instillation.*—Hydrochloric acid (0.4 per cent) was instilled (Walpole) over an interval of 15 to 46 days in four dogs, 82 to 108 cc. per hour being allowed to run into the fasting stomach by the drip gravity method through a gastrostomy opening. The instillations were made daily for six and a half to seven hours. The animals were fed late in the day, after the instillation was discontinued. No ulcers occurred in dogs. Samples removed periodically for titration indicated that during the time of acid installation an average acidity of 73 degrees of free hydrochloric acid was maintained in the stomach.

In three of four cats, similarly treated, but given only 40 to 50 per cent as much acid, ulcers were produced in four to 11 days. One cat pulled the gastrostomy tube out on the third day and presented no changes in the stomach, duodenum or esophagus. Ulceration in the cardiac esophagus, fundus, antrum and duodenum was a common finding in the other animals. This finding will be described in greater detail at a later date.

*The Production of Ulcers by Subcutaneous Implantation of Histamine in Beeswax.*—Dr. Charles F. Code, Assistant Professor of Physiology at the University of Minnesota, whose studies on histamine assays in body fluids are well known, wished to study the effects of subcutaneous implantation of histamine in beeswax upon the gastric secretory mechanism in dogs. The results of this study will be reported later (Code and Varco). This type of histamine poisoning succeeds in pouring out extraordinary quantities of a

highly concentrated acid. A concentration of 170 degrees (0.62 per cent HCl) has been maintained in the secretion of a Pavlov pouch more than one hour, and a liter of N/10 HCl will be secreted in 24 hours by such a pouch under the powerful stimulus of gradual liberation of histamine.

Histamine in beeswax (20 mg. of the base, equivalent to three times this amount of histamine as ergamine acid phosphate) was implanted into the back muscles at several sites in five cats (Walpole). Ulcers occurred in all in three to nine days—large and small erosions as well as perforating ulcers were observed (Fig. 9).

*Antral and Fundic Extracts and Their Effect upon the Gastric Secretory Mechanism.*—The gastric theory of gastric secretions rests on Edkins' work with pyloric and fundic extracts of gastric mucous membrane and their effect upon the secretory capacity of the cat's stomach. Much work has been done on this phase of the problem by many observers. One of us (Trach), working in collaboration with Dr. C. F. Code, of the Department of Physiology, has prepared histamine-containing and histamine-free extracts of the antral and fundic mucous membrane of both dog and man. In the main, these observations suggest that the histamine-containing extracts, whether from the antrum or the fundus, of both dog and man, exert a stimulating effect upon the secretory capacity of Pavlov and Heidenhain pouches in dogs, as well as upon the intact stomach of the dog. Histamine-free preparations were without effect. These findings will be reported in greater detail at a later date.

Code has determined the histamine content, per gram of antral and fundic mucosa, in both dog and man. He found a larger content of histamine, per unit of mucosal weight, in the fundus for both man and dog. Code also found that the dog's gastric mucosa contains considerably more histamine, per unit of weight, than does man's gastric mucosa. Code's observations on the histamine content of the gastric mucosa of dogs confirm the observations of Gavin, McHenry and Wilson, who found that 80 per cent of the total histamine is to be found in the fundus.

Gastric tissue, it is to be remembered, unlike intestinal mucosa which contains both histamine and histaminase, contains no histaminase. It has already been suggested (Dragstedt, C. A., and associates, 1940) that alcohol mediates its stimulating effect upon gastric secretion by the liberation of histamine. We, too, have noted that alcohol, when instilled into jejunostomy, enterostomy, cecostomy, or colostomy openings in man, exerts a stimulating effect upon gastric secretion in responsive stomachs in man. Similarly, we observed that veal broth instilled into jejunostomies in man excites the gastric secretory mechanism.

*Responsiveness of Antral, Fundic (Pavlov and Heidenhain) Pouches and the Residual Stomach (after Establishment of Gastro-intestinal Continuity) to Introduction of Alcohol.*—Sawitsch and Zeliony (1913) observed that a greater secretion of hydrochloric acid was obtained from the stomach when food came in contact with antral mucosa. Lim, Ivy and McCarthy

(1925) confirmed this observation and state that antral mucosa is definitely more sensitive in evoking the stimulus for hydrochloric acid secretion than is contact of food with fundic mucosa. These conclusions constitute a bit of evidence which lends tenable support to the Edkins' hypothesis. We have seven dogs with antral and fundic pouches in addition to the residual stomach. Into these pouches 25 cc. of a 7 per cent solution of alcohol has been introduced. Our experiments are incomplete. On surveying our data, we were inclined, at first, to believe that the observations of Sawitsch and Zeliony, and Lim, Ivy and McCarthy were supported by our findings. A typical response is indicated in Table XI. It is to be noted that a greater secretion was obtained from the Pavlov pouch. But there is no evidence of stimulation *over* the secretion obtained in the fasting state. It is to be remembered, further, that the amount of acid secreting tissue in our antral pouches is

TABLE XI  
RESPONSE OF ANTRAL AND FUNDIC POUCHES TO INTRODUCTION OF ALCOHOL

*Dog No. 108—Oscar:*  
*Procedures*  
*Antral and Pavlov pouches*

Date of Gastric Analysis	Residual Stomach					Antral Pouch				
	Degrees		Volume Cc.	Mg. HCl in	Mg. HCl in	Degrees		Volume Cc.	Mg. HCl in	Mg. HCl in
	Free Acid	Total Acid		Free Acid	Total Acid	Free Acid	Total Acid		Free Acid	Total Acid
<i>4/22/40</i>										
Fasting—1 hr.	0	8	4.0	0	1.17	0	8	1.0	0	0.29
Fasting—2 hrs.	0	42	5.5	0	8.4	0	33.3	0.9	0	1.09
25 cc. 7% alcohol placed in Pavlov pouch— $\frac{1}{2}$ hr.	18	36	13.0	8.54	17.0	0	43	0.7	0	1.09
1 hr.	0	32	3.2	0	3.7	0	100	0.3	0	1.09
<i>4/23/40</i>										
Fasting—1 hr.	0	40	10.5	0	15.3	43	150	0.9	1.41	4.9
25 cc. 7% alcohol placed in antral pouch— $\frac{1}{2}$ hr.	0	10	8.0	0	2.92	30	40	1.2	1.31	1.75
1 hr.	0	23	4.8	0	3.27	50	60	0.7	1.28	1.52

relatively small. It may be pointed out here that instillation of alcohol into the residual gastric pouch (ref. Table IX, under item IV) elicited a good response from the Pavlov pouch. In the light of the greater histamine content of fundic mucosa, one could expect, reasonably, a greater response upon the residual stomach from instillation of alcohol into fundic rather than antral pouches.

The responsiveness of the antral and fundic mucosa to contact with alcohol or food, with reference to the secretion of acid, is an important item. Should the antral mucosa prove to be definitely more sensitive, one bit of evidence would continue to support the Edkins' hypothesis.

SUMMARY.—These observations are not intended as suggestions upon which the indications, for the various gastric operations for the relief of

ulcer, should be formulated. Many items enter into consideration which determine choice of operative procedures, and, frequently, standardized indications fail to meet optimally the requirements of a given patient. However, the observations related here have some importance in determining what may be expected reasonably of certain types of operative procedures.

Satisfactory operations for ulcer insure: (1) Achlorhydria to maximal stimulation (histamine); and (2) decreased emptying time. Operations which fail to afford real promise of achlorhydria leave too much to chance and hold out too great a risk of gastrojejunal or recurrent ulcer, to stamp them as satisfactory operations to be invoked frequently for the surgical relief of ulcer. Gastrojejunostomy and excision of the pylorus and antrum fall into this class.

Gastrojejunostomy (and probably also, gastroduodenostomy and pyloroplasty) exerts its value through quickening of the gastric evacuation time. Removal of the pylorus and antrum whether by the Billroth I or II plan is probably of no great consequence) is attended by true achlorhydria only occasionally. The virtue of this procedure lies largely, also, in diminution of the emptying time.

Extensive gastric resection when accompanied by gastrojejunostomy is attended usually by achlorhydria to histamine stimulation. When, however, three successive doses of histamine are given, some such gastric pouches, previously achlorhydric, may secrete free hydrochloric acid. True achlorhydria is reported after extensive gastric resection, tubular resection of the corpus and antrum, accompanied by gastrojejunostomy leaving the pylorus and antrum intact), and after the antral exclusion resection save for the recent cases).

The items necessary to afford real promise of achlorhydria are (1) extensive excision of the acid secreting area; and (2) provision for gastrojejunostomy. Occasionally true achlorhydria follows performance of operation directly; in a number of instances a few months must elapse before achlorhydria occurs. Operations which delay the gastric evacuation time (such as provision for complete intragastric regurgitation) are not likely to be followed by achlorhydria and may, like anastomotic operations which lower gastric evacuation time without lowering gastric acidity, be followed by a high incidence of recurrent ulcer.

It is pointed out that the size of the resection is an important item in determining whether true achlorhydria will occur. The term "subtotal gastric resection"\* has been applied by many experienced gastric surgeons, when their own diagrams indicate that they excise in the vicinity of 50 per cent of the total gastric tissue. The surgeon, intent on affording his patient maximal protection against recurrent ulcer, must take more serious account of the amount of gastric tissue which he removes. The minimal amount necessary to excise to afford real promise of achlorhydria is not known. Excision of

\* A satisfactory definition of "subtotal" is a little less than all. No resections of less than 80 per cent can be described reasonably as "subtotal."



66 to 80 per cent usually suffices. Whether achlorhydria *per se* carries special risks for the patient remains to be seen.

On the clinical side, the data reported herein appear to indicate that the Edkins hypothesis, of control of the gastric phase of gastric secretion by a pyloric and antral hormone, is invalid. The essence of this proof lies in two occurrences: (1) The consistent production of true achlorhydria in five patients having duodenal ulcer after tubular resection of the corpus and fundus attended by gastrojejunostomy, leaving the pylorus and antrum intact (Group 6). (2) Failure to produce true achlorhydria in patients with excision of the pylorus and antrum (Group 2). Another item bearing directly upon the point in question, but upon which our evidence is not yet complete, is the group of patients in which extensive gastric resection has been performed, but in which the pylorus and a small fragment of the antrum are left (Group 4).

The importance of "night secretion" in this relatively long fasting period is pointed out. It often breaks the effectiveness of dietary control of the ulcer regimen.

On the experimental side, it is indicated that sacrifice of the pylorus and antrum does not diminish the secretory activity of fundic (Pavlov and Heidenhain) pouches. In time, the residual gastric pouch, after antral excision, tends to become achlorhydric. Whether this occurrence is owing largely to impaired gastric secretory capacity, consequent upon gastric resection and provision for intragastric regurgitation, or whether the occurrence is influenced significantly by sacrifice of the antrum, cannot be stated definitely.

On the item of the relative responsiveness of antral and fundic mucosa to the presence of alcohol, our findings are incomplete and inconclusive. Previously recorded data on this score suggest a greater sensitivity of the antral mucosa—an observation which would lend at least partial support for the Edkins' theory of gastric secretion.

The experimental production of ulcer (exogenous) in cats by the introduction of 0.4 per cent acid is reported. (See Walpole et al.) Similarly, the intramuscular implantation of histamine in beeswax (Code) is followed by maximal stimulation of hydrochloric acid secretion, and ulcer can be produced regularly in cats by this method (endogenous). These latter observations lend increased significance to the acid factor in the genesis of ulcer.

Extracts of gastric mucosa, prepared from the stomachs of dog and man, which contain histamine stimulate the secretion of hydrochloric acid in dogs with fundic pouches. Such activity was demonstrated in the extracts prepared from both antral and fundic mucosa. The mucosa of the fundic zone contains more histamine, per unit of weight (per gram), than does antral mucosa (Code) and the dog's gastric mucosa contains more histamine, per unit of weight, than does the gastric mucosa of man.

#### CONCLUSIONS

- (1) Anastomotic operations performed for ulcer fail to produce achlor-

hydria. The virtue of such operative procedures is mediated through lessening of the gastric evacuation time.

(2) Extensive gastric resection *per se* is not followed by achlorhydria, but when accompanied by gastrojejunostomy, achlorhydria follows, usually with the lapse of time.

(3) Provision for complete intragastric regurgitation lengthens the gastric phase of gastric secretion and is undesirable.

(4) Excision of the pylorus and antrum in man for ulcer is rarely attended by achlorhydria.

(5) Achlorhydria may accompany extensive gastric resection for ulcer, when the pylorus and antrum remain.

(6) The Edkins' hypothesis on the clinical side, on the basis of our observations, appears to be invalid. On the experimental side, our observations are still incomplete, save that excision of the pylorus and antrum does not decrease the secretory capacity of fundic pouches.

(7) The importance of the acid factor in ulcer is emphasized in the occurrence of ulcers in cats after intragastric instillation of 0.4 per cent HCl and after subcutaneous intramuscular implantation of histamine in beeswax.

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DISCUSSION.—DR. LESTER R. DRAGSTEDT (Chicago, Ill.): Doctor Wangensteen and his associates deserve our congratulations and thanks for their extensive and painstaking study of the effects of various operative procedures on the physiology of the stomach. It is the kind of information that should have been available many years ago and would have made unnecessary many a surgical experiment on patients with gastric and duodenal ulcer. I do not share the pessimistic view of the ulcer problem expressed by Doctor Ivy in 1931. The vast amount of work done on the lower animals in a large number of laboratories during the past few years has so greatly clarified and extended our knowledge in this field that there are few diseases where our information is more complete.

A typical, chronic progressive ulcer can be produced at will in the dog and the factors necessary for its production are fairly well understood. Pure undiluted gastric juice has the capacity to digest away all living tissue, including the wall of the stomach itself, and an ulcer may be expected whenever opportunity for prolonged contact between such a secretion and the mucosa occurs. The normal stimulus for gastric secretion is the ingestion of food, and this food promptly reduces the acidity and pepsin concentration of the fundus secretion. In many ulcer patients, however, copious secretions of gastric juice occur without the stimulus of food, often during the night, and large amounts of pure gastric juice remain in contact with the gastric and duodenal mucosa for long periods. Solution of the clinical problem would seem to depend upon the discovery of the nature of this abnormal stimulus for gastric secretion.

The interpretation of Doctor Wangensteen that reduction of the acidity of the gastric content following partial gastrectomy, gastrojejunostomy, gastroduodenostomy, and similar procedures, is due to lessening of the gastric phase of secretion through more rapid emptying of the stomach seems well justified by the evidence presented. The new procedures of attempting to reduce the acidity by actual removal of large areas of the acid-secreting fundus are interesting, and it is important that they should be explored by investigators like Doctor Wangensteen and his associates, who are willing, also, to study the effects of these operations on gastric physiology.

The fact that subtotal gastrectomy is occasionally necessary to cure the disease does not indicate that this procedure is the solution to the problem, but it is only a confession of our inability in many cases to control the excessive gastric secretion by less radical measures.

DR. ROSCOE GRAHAM (Toronto, Can.): Gastro-enterostomy has been followed by relief of symptoms of duodenal ulcer in spite of the operation. A restudy of a series of our patients has shown of those symptom-free, 47 per cent had malfunctioning stomata.

Doctor Wangenstein's contribution is excellent, but it is doubtful whether the relation of acid to recurrent ulceration is still settled. While we have deleted the necessity of operation from the treatment of an uncomplicated duodenal ulcer, we are adding further confusion. Such confusion arises because in reports of operated cases there is not an accurate description of the extent of the resection and the type of reconstruction of the gastro-intestinal tract. Our clinical experience has borne out Doctor Wangenstein's statement—"If we must operate upon patients suffering from complicated duodenal ulcer, such operation should be a radical gastric resection." Doctor Dragstedt says it is an admission of defeat. It is! It is an unphysiologic compromise, which, however, if applied to properly selected cases, produces a happy result, and until we can determine accurately the cause of ulcer, must be an acceptable therapeutic procedure. May we, as a group, in reporting the results of our gastric resections for duodenal ulcer, state accurately the extent of the resection and the method of reconstruction. This, I trust, will avoid many years of confusion and error in arriving at an accurate evaluation of surgical therapy for duodenal ulcer.

DR. J. SHELTON HORSLEY (Richmond, Va.): Studies of the kind that Doctor Wangenstein and his associates have reported are always interesting. Much gastric surgery has been performed without the proper consideration of the underlying biologic principles. Physiologists have shown that in experimental animals a large portion, often more than 75 per cent, of normal kidney tissue can be removed, if undertaken in different stages, with no apparent permanent interference with the function of the kidney. The same is true of the liver. If more than this maximum amount is excised there may not be enough tissue left to undergo sufficient hyperplasia, and function may, therefore, be permanently affected. It would seem probable that this general law of compensation applies to the stomach, and doubtless accounts for the disappointing late results that follow many operations of so-called fundectomy, or excision of a large quantity of the acid-bearing region of the stomach.

The efficacy of operations on the stomach cannot always be evaluated by the amount of hydrochloric acid in the gastric contents. It is not as simple as that. If, for instance, the estimation of acid in the gastric contents is made before there is opportunity for hyperplasia of the acid-forming cells of the remaining portion of the stomach, naturally the acid will be low or absent. In Doctor Wangenstein's cases there was, I believe, achlorhydria, at some stage, in all of the cases that he reported. Then, too, it is probable that some individuals will have a tendency to compensate for the destruction of the acid-bearing part of the stomach more readily than others. Almost any subtotal resection would leave approximately at least one-fourth of the acid-secreting portion, and, as an analogy between this and the experimental work on the kidneys and liver, it would seem that the remaining portion is capable by hyperplasia of eventually restoring practically the full amount of acid. Other features that enter into the results of gastric operations are the

type of operation performed, and the portion of the intestinal tract into which the gastric contents empty. If, for instance, a Billroth II type of operation is undertaken and an entero-enterostomy performed, much of the alkaline contents of the duodenum is diverted and does not reach the gastric anastomosis. This is, in a sense, the duodenal drainage of Mann and Williamson, which has been found experimentally to result in an ulcer at the site of the anastomosis in almost every instance. Of course the entero-enterostomy does not necessarily drain off all of the alkaline contents, so that the analogy is not complete, but it, at least, takes away some of it and so weakens the resistance of the gastric anastomosis to the acid that is left.

It has been shown by physiologists that the sensitivity of the intestinal mucosa to the acid of the stomach increases from the duodenum down to and including the large intestine. The duodenum ulcerates more frequently because it bears the first brunt of the impact of the acid from the stomach, but an anastomosis with the jejunum, even when there is no entero-enterostomy, entails a greater probability of ulceration from the acid of the stomach than would occur with the same amount of gastric acid emptying into the duodenum.

DR. OWEN H. WANGENSTEEN (Minneapolis, Minn., closing): In my presentation, I had no opportunity to allude to the experimental production of ulcer. During the past year, my colleagues and I, with the cooperation of Dr. C. F. Code, Assistant Professor of Physiology, have been exploring some phases of this problem. The daily instillation of 0.4 per cent hydrochloric acid in fairly large amounts over a period of some hours into the stomach of the dog was not followed by the occurrence of ulcer. When, however, similar instillations, but in less amounts, were made into the stomachs of cats, ulcers were produced quite uniformly. Employing a suggestion of Doctor Code that histamine be embedded in beeswax, to permit constant liberation of the histamine, and implanted intramuscularly, ulcers were uniformly produced in cats as well as in the two dogs upon which the experiment has been tried to date. Doctors Cole and Varco have studied the effect of such gradual liberation of histamine upon the secretory capacity of gastric pouches. The effect is profound, high concentrations of hydrochloric acid (0.6 per cent) being poured out in large amounts. I have the impression that we may be able to produce ulcer experimentally by this method in every animal whose stomach secretes hydrochloric acid. We propose to probe this problem further. For therapeutic reasons, it is most important to know whether acid is *the* factor or only *an important* factor in the spontaneous occurrence of ulcer in man.

Mind you, it takes only a little wisp of actively secreting gastric mucosa to produce an ulcer. We need only recall what may happen in Meckel's diverticulum, where a bit of gastric mucosa, no larger in area than the thumbnail, may produce hemorrhage or perforation, as is seen more frequently in duodenal or gastric ulcer.

Doctor Horsley referred to the regeneration of gastric mucosa. The regenerative property and capacity of gastric mucosa is well known. When I stated that we removed by *measurement* 66 to 80 per cent of the stomach, I admit freely that this measurement probably does not constitute this same fraction of the gastric mucosa. As you know, the mucosa of the upper portion of the stomach is considerably more rugated than the antral portion. When, at operation, one leaves a small residual gastric pouch which would hold approximately four ounces of fluid (120 cc.) and a few months later, one sees that small residual gastric pouch expanded into a stomach of much

larger proportions, I like to think that the following has happened: Smooth muscle has an enormous capacity for adjusting itself to various degrees of stretch (one need think only of what happens quite normally in the stomach, bowel and bladder); the small residual gastric pouch, even in the absence of obstruction, enlarges to the extent that the mucosa and submucosa will permit the smooth muscle of the stomach to stretch.

So that whereas excision of the amount of stomach described in this presentation appears large, it is to be remembered that the same percentage of the gastric mucosa is not sacrificed.

Patients who have been achlorhydric to histamine, persistently during the early months after operation, have not in our experience exhibited free hydrochloric acid later. The use of continuous suction rather than intermittent aspiration diminishes the possibility of not getting *true* acid values from the gastric juice. Even with the employment of suction it is clear that all the gastric juice cannot be aspirated—hence the weakness of single aspirations.

It is interesting that provision for *some* intragastric regurgitation must be made to produce achlorhydria to histamine stimulation after gastric resection. It would appear that total intragastric regurgitation of the duodenal content is undesirable. *How much* intragastric regurgitation is optimal is not yet apparent. It may prove that the intragastric regurgitation which an ordinary stoma provides is optimal. We have been exploring this query in part by adding entero-anastomoses to some of the extensive gastric resections. An advantage of entero-anastomosis is that it does away with the mechanical derangements at the stoma after gastrojejunal anastomosis—disturbances which are familiar to everyone. I must emphasize, however, that I do not suggest that entero-anastomosis be performed in the ordinary small gastric resection. My colleagues and I do not feel that our findings should be interpreted as indications for choice of operative procedure. What we do mean to point out is what the surgeon may reasonably anticipate from alternative types of operation.

It is extraordinarily interesting that the residual stomach may become persistently achlorhydric to histamine stimulation after gastric resection and gastrojejunal anastomosis of the extent which I have described, for, after all, a sizable fragment of gastric mucosa remains still. Dr. Maurice Visscher, Professor of Physiology, with whom I have had many profitable discussions upon the ulcer problem, asked if it was reasonable to believe that one could make the stomach achlorhydric to maximal stimulation (histamine) as long as gastric mucosa remained. It appears that we can.

The surgeon, when operating for ulcer, must be studious in his effort not to inflict upon the patient a worse disorder than that with which the patient came to him. The operation which fails to reduce gastric acidity leaves a great deal to chance and invites the possibility of a recurrent ulcer.



## DIAGNOSIS AND SURGICAL MANAGEMENT OF LEIOMYOMATA AND LEIOMYOSARCOMATA OF THE STOMACH\*

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AS POINTED OUT by Sworn and Cooper, leiomyomata, said by Boyd (1938) to be the commonest benign tumors of the stomach, receive scant attention in most text-books and are referred to by Romanis and Mitchiner (1937) as usually causing no symptoms whatsoever. In a review of the



FIG. 1.—Case 1: Roentgenogram of the stomach showing the defect.

literature of benign tumors of the stomach, Minnes and Geschickter found that leiomyomata formed 36.6 per cent of all benign tumors of the stomach. Two years later, Chaffin noted the increasing incidence of smooth muscle tumors of the stomach, recording 363 cases that had been reported to date,

\* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.



and in the same year Collins and Collins placed the incidence of leiomyomata at 39.9 per cent of all gastric benign tumors. In the study of benign tumors of the stomach made by Eliason and Wright, 60 per cent were leiomyomata. The fact that benign tumors of the stomach, in general, are not infrequent, is shown by the fact that Rigler and Ericksen, in 6,742 autopsies performed in four years at the University of Minnesota, found benign tumors formed 26 per cent of all gastric neoplasms.

Regarding their etiology little can be definitely proven. It has been stated by more than one writer that unchecked smooth muscle proliferation



FIG. 2.—Case 1: Note, on the gross specimen, the scars of healed ulcerations over the tumor.

during the healing phase of gastric ulcer may be an originating factor in this condition.

The sex incidence of these tumors is about equal—in our seven cases, four men and three women. The average age of 529 reported cases was 53.6 years; in our cases, 44 years.

Rudolf Virchow (1863) was the first to classify gastric leiomyomata pathologically. He divided them into internal (submucous) and external (subserous). That this classification, though crude, has an important bearing on the symptomatology produced by these tumors can readily be seen in the histories in our cases, all of which were intragastric.

There are no definite laboratory findings in these cases except anemia,



FIG. 3.—Case 1: Photomicrograph of portion of stomach wall showing infiltrating tumor. At top and bottom, tumor cells are seen in cross-section; in central portion of muscularis, in longitudinal-section. Cells tend to be spindle-shaped. Intercellular substance absent. Malignant tumor, probably atypical leiomyosarcoma. ( $\times 270$ )



FIG. 4.—Case 2: A recent photograph.

and there is no relationship to gastric acidity. The lowest hemoglobin in our cases was 36, the highest 88, and the average 63. The lowest red blood count was 2,200,000, the highest 4,500,000, the average 3,100,000. Reliance in diagnosis must be placed upon the roentgenologic findings, plus an appreciation of the occurrence and clinical importance of these tumors. They are most commonly found in the lower portion of the stomach, and the incidence of involvement of the two curvatures is about equal. Chaffin reports the most characteristic roentgenologic finding as being relatively clear rugae and undisturbed peristalsis in the immediate neighborhood of the tumor. The

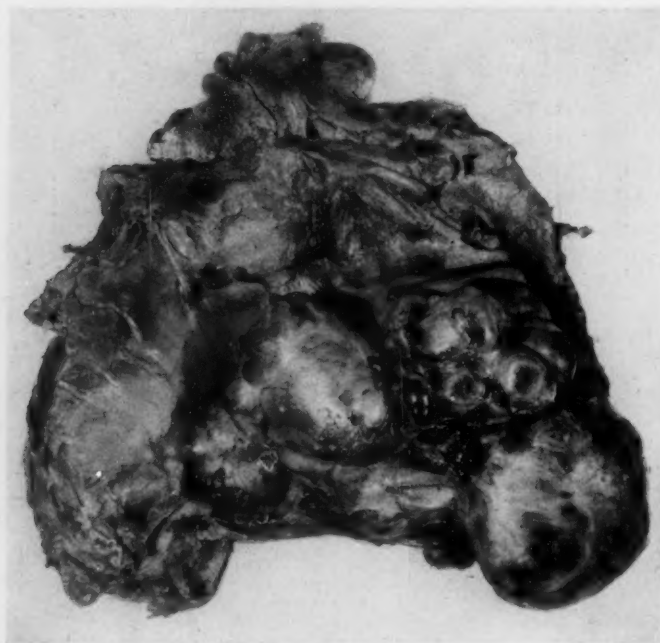


FIG. 5.—Case 2: A photograph of the entirely removed stomach, with the stomach opened, showing the leiomyosarcomatous masses occupying most of the stomach.

outline defect made by the more or less spherical tumor was the most common roentgenologic finding in our cases. The pedunculated tumors are, of course, movable on palpation and not infrequently cause pyloric obstruction. Matas has reported a pedunculated leiomyoma acting as a ball valve.

The third most important fact of clinical importance regarding these gastric tumors (the first two being hemorrhage and obstruction) is malignant degeneration. As we review our cases it seems probable that they all originated in a leiomyoma originally benign. The fact that Collins and Collins found 54 recorded cases of malignant leiomyomata of the stomach indicates that malignant change in these benign gastric tumors is probably more common than supposed.

Of seven patients operated upon in our clinic for leiomyomatous tumors

## GASTRIC LEIOMYOMA AND LEIOMYOSARCOMA

of the stomach, five, or 71 per cent, showed sarcomatous degeneration. This is undoubtedly a high average. (The average hemoglobin in the seven cases, when first seen, was 63 per cent, and the average erythrocyte count 3,100,000.) The average time after the beginning of symptoms (largely hemorrhage) attributable to the tumor when these patients were seen and operated upon was 17 months. Five of the seven patients had had hematemesis or tarry stools: one for three weeks, one for four weeks, one for 18 months, one for four years, and one for 30 months.

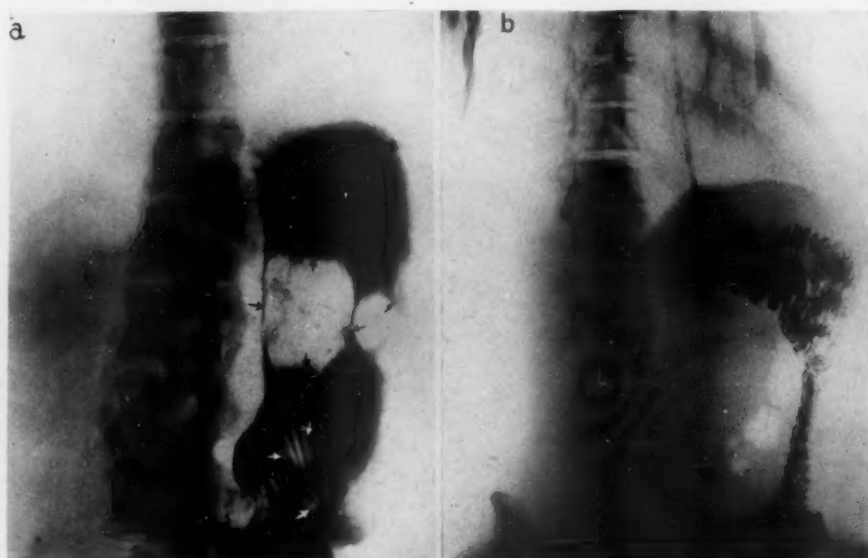


FIG. 6.—Case 2: (a) Roentgenogram of the stomach showing the tumor masses occupying most of the stomach. (b) A postoperative roentgenogram showing the jejunum anastomosed to the esophagus. Note the long antecolic loop of jejunum without an entero-enterostomy, and how well it functions.

Because of the reported incidence (36 per cent of all benign tumors of the stomach, Minnes and Geschickter) of leiomyomata, because of the high percentage of malignant degeneration (five out of seven in our cases), because of the high grade of secondary anemia present when the patients presented themselves for treatment, and because of the relatively long histories likewise present when these patients first appeared for surgical treatment, it seems desirable to call attention, in a brief and simple way, to this relatively small but important group of gastric tumor cases.

From our experience with this small group of cases and from the reports in the literature, it may reasonably be said that leiomyomata of the stomach are not rare, that the predominating intragastric types tend to become ulcerated on their surfaces (Figs. 2, 12 and 15), and to produce hematemesis or melena; that they may or may not produce digestive symptoms; and that they possess real dangers of sarcomatous degeneration. It should be realized that ulceration of the surface and into the substance of these tumors is a

quite common complication with them, and that in any patient with hematemesis or melena the possible presence of an ulcerated leiomyoma should be kept in mind and searched for in gastric roentgenologic examinations to explain gastric bleeding.

From the experience with these seven cases, we can say that there is nothing characteristic in these tumors, when they are single and discrete, whereby one may foretell with certainty, either roentgenologically, by gastroscopy, or even on direct visualization, whether or not sarcomatous degeneration has already taken place. When the tumors are multiple and have

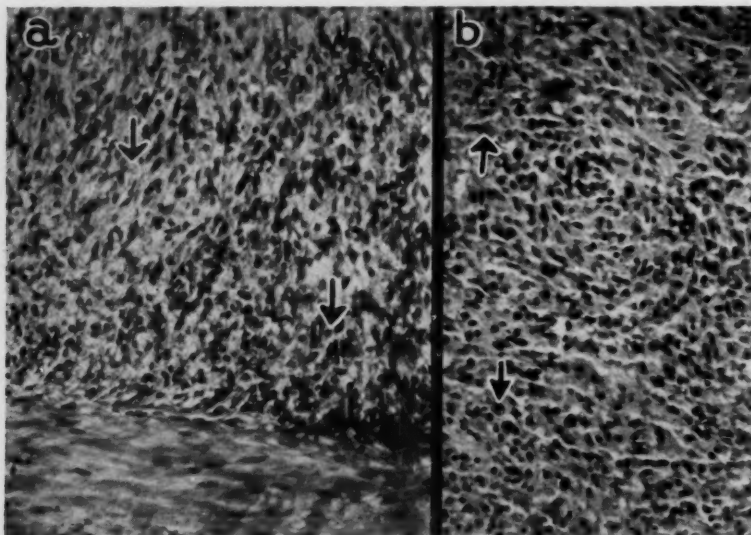


FIG. 7.—Case 2: (a) Photomicrograph of portion of leiomyosarcoma removed in 1933, showing spindle character of cells and scattered giant cells. ( $\times 300$ ) (b) Essentially similar picture. Tumor removed in 1937, showing slightly greater cellularity. Leiomyosarcoma. ( $\times 300$ )

involved the entire stomach, as was the case in the patient submitted to total gastrectomy (Case 2, alive and well now three and one-half years), one can, of course, reasonably assume that sarcomatous degeneration has already taken place, as was the case in this patient.

#### CASE REPORTS \*

**Case 1.**—Hosp. No. 40230: A male, age 39, was first seen at the clinic, May 17, 1934, because of profuse gastric hemorrhages. The first one had occurred a year and one-half previously, at which time he vomited "several quarts" of fresh blood. Two months before admission he had had a second profuse intestinal hemorrhage, and one month before, a third. He had lost 12 pounds and his hemoglobin was 65 per cent. Roentgenograms revealed an egg-sized tumor projecting into the lower portion of his stomach with ulceration on its surface. At operation, a large movable tumor, 8 cm. in diameter, was found just proximal to the pylorus, on the greater curvature. Subtotal resection was performed and he made an uneventful convalescence. The pathologic report showed atypical leiomyosarcoma of low malignancy.

\* The pathologic diagnoses of the tumors were made by Dr. Shields Warren, Pathologist to the New England Baptist and New England Deaconess Hospitals.



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In a report from the patient, dated April 4, 1940, he had had no further hemorrhages, was getting along well, and working every day.

**Case 2.**—Hosp. No. 72221: A female, age 27, had been treated for several years for

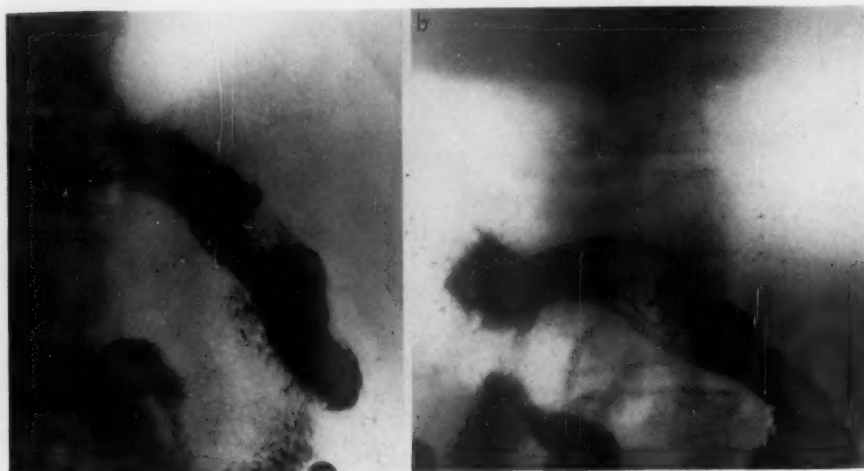


FIG. 8.—Case 3: (a) Note the typical roentgenographic defect; (b) note the completeness of the outline of the tumor in the roentgenogram. This is no guarantee of the absence of malignancy.

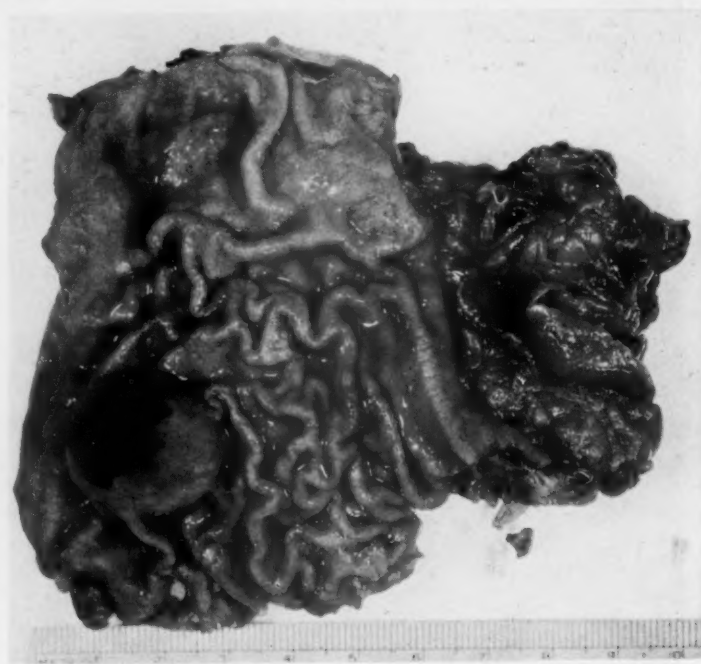


FIG. 9.—Case 3: The gross specimen shows the typical intragastric leiomyoma.

a secondary anemia of unknown origin. Four years before admission she had had a profuse hemorrhage from her mouth associated with tarry stools. At that time, December 7, 1933, she was operated upon elsewhere, and her stomach was found to contain multiple

lobulated tumors along the lesser curvature. The lower group of tumors only were excised. The pathologic report was leiomyoma. Following operation she continued to run a considerable degree of anemia associated with repeated and rather alarming hemorrhages.

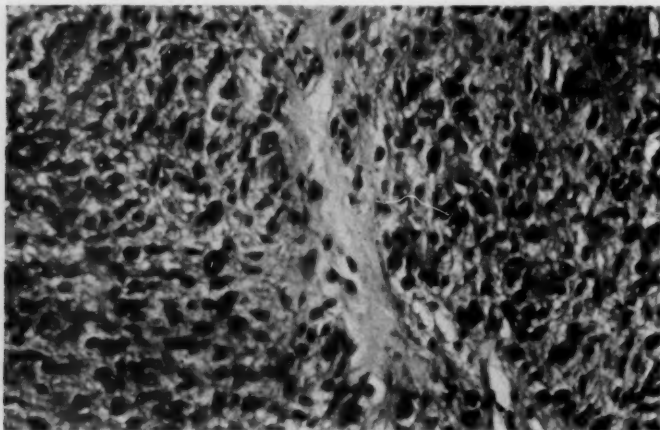


FIG. 10.—Case 3: Photomicrograph of portion of leiomyoma showing well-defined smooth muscle cells with some supporting stroma. Moderate variation in nuclear size. No evidence of malignancy. ( $\times 300$ )

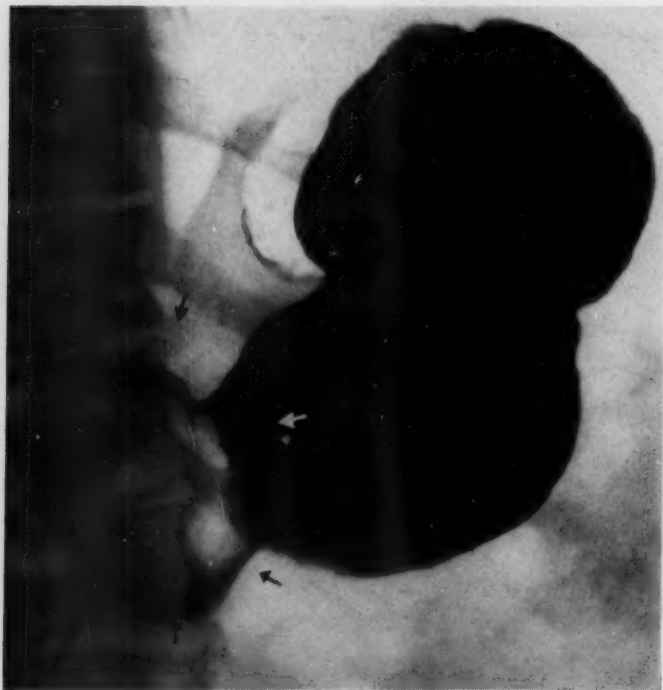


FIG. 11.—Case 4: Note large gastric defect as shown roentgenographically.

At her admission to the clinic, October 8, 1937, her hemoglobin was 53 per cent, and her red cell count 3,460,000. Roentgenologic examination revealed several intraluminal filling defects in the stomach, occupying most of the cardiac portion of the stomach, the

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largest of which measured 7 cm. on the film, and came within one inch of the cardiac end of the esophagus. This finding was verified at operation. Total gastrectomy was performed, October 18, 1937. The pathologic diagnosis was leiomyosarcoma.

This patient reports, April 6, 1940, that she has married in the past year, that she is



FIG. 12.—Case 4: Note the ulceration over the tumor—a finding present in many of these cases and obviously the explanation of the frequency of hemorrhages in patients with this type of gastric tumor.

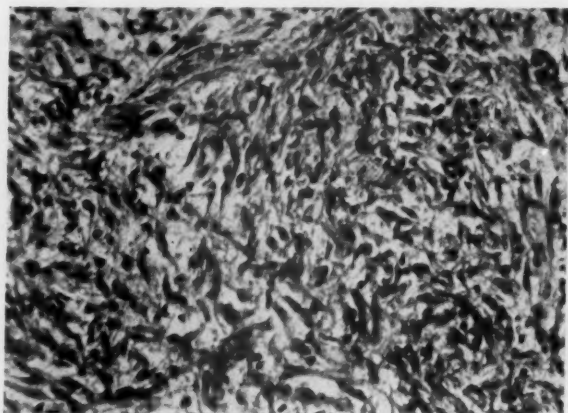


FIG. 13.—Case 4: Portion of less differentiated part of leiomyosarcoma of low malignancy showing elongated smooth muscle cells with irregular nuclei. Tissue fairly edematous. (X300)

well in every way and maintains her weight and blood picture. She receives iron, liver and hydrochloric acid and pepsin. She eats without difficulty.

**Case 3.**—Hosp. No. 75739. A male, age 60, came to the clinic, February 10, 1938, because of indigestion for 15 years. He had noticed attacks of vertigo and faintness for

the last six years, accompanied by diarrhea on several occasions. A roentgenogram a year previously had shown a polyp of the stomach. His hemoglobin was 88 per cent, and erythrocyte count 4,480,000. Roentgenologic examination revealed a filling defect in the lesser curvature. The tumor appeared to have a rather broad base. At operation,



FIG. 14.—Case 5: Note the large roentgenographic defect made by the tumor.

May 31, 1938, a circumscribed polypoid mass, 5 cm. in diameter, was found, which projected partly through the serosa of the stomach in the pyloric region. Subtotal gastrectomy was performed. The pathologic report was leiomyoma.

**Case 4.**—Hosp. No. 80367: A male, age 51, was seen at the clinic, June 17, 1938, because he had suddenly begun to pass dark stools three weeks previously. This had continued, and at the time of admission he felt quite weak. His hemoglobin was 72 per cent and his erythrocyte count, 2,176,000. A roentgenogram showed a large filling defect in the pyloric region of the stomach. At operation, June 22, 1938, a large tumor, 10 cm. in diameter, was found just proximal to the pylorus and a subtotal gastrectomy was performed. The pathologic report was leiomyosarcoma.

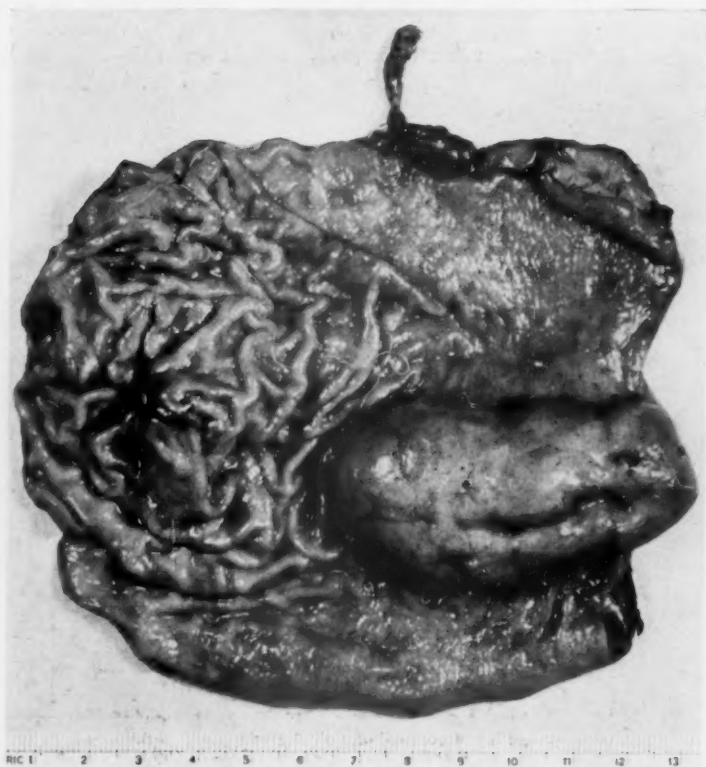


FIG. 15.—Case 5: Note, in the gross specimen, the healed scar over the tumor indicating the tendency for these tumors to ulcerate and bleed.

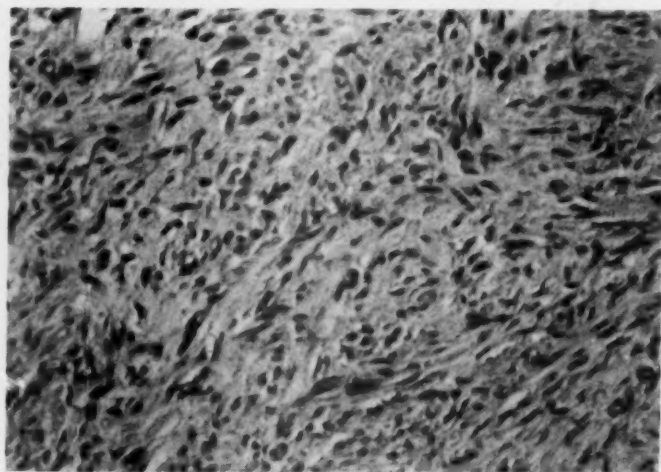


FIG. 16.—Case 5: Photomicrograph showing portion of leiomyoma (benign) with well-differentiated smooth muscle cells. Note elongated, mature character of the nuclei and fairly orderly arrangement of cells. ( $\times 300$ )



A letter from the patient, dated April 4, 1940, stated that he was well in every way and had had no more hemorrhages. He is maintaining his weight and working regularly.

**Case 5.**—Hosp. No. 95855: A male, age 40, came to the clinic, May 17, 1939, and stated that he had first noted black stools a year and one-half previously. Nine months ago he had had a severe hemorrhage which forced him to bed for three weeks. In spite of a Sippy diet and ulcer regimen he had had a third hemorrhage three weeks before



FIG. 17.—Case 6: The gross specimen divided and shown in cross-section.

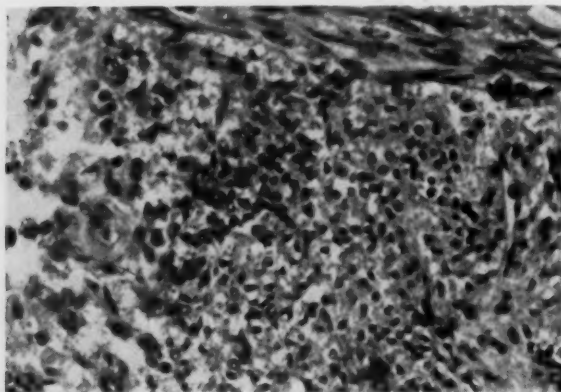


FIG. 18.—Case 6: Photomicrograph of portion of leiomyosarcoma showing many cells in cross-section, some in longitudinal section. Note the large size of some nuclei. Low grade malignancy. ( $\times 500$ )

admission. His hemoglobin was 58 per cent and erythrocytes numbered 3,670,000. Roentgenologic examination revealed a filling defect involving the prepyloric area on the lesser curvature of the stomach. At operation, September 8, 1939, a soft mass, approximately 5 cm. in diameter, was found in this region. Subtotal gastrectomy was performed. The pathologic diagnosis was leiomyoma.

The patient reported personally, April 5, 1940, and is well in every way.

## GASTRIC LEIOMYOMA AND LEIOMYOSARCOMA

**Case 6.**—Hosp. No. 97271: A female, age 47, came to the clinic, October 3, 1939, stating that four weeks before admission she had suddenly vomited a profuse amount of blood. She was taken to a hospital where she had three more hemorrhages and five transfusions during a period of two weeks. Her hemoglobin was 67 per cent, and erythrocytes numbered 3,410,000. A roentgenogram revealed a large mass in the fundus of the stomach arising from the superior medial wall. At operation, October 6, 1939, a large, freely movable mass was found arising from the cardia near the esophagus. The mass was pedunculated and submucous excision was performed. The pathologic report was leiomyosarcoma of low malignancy.



FIG. 19.—Case 7: The gross specimen shown in the removed portion of the stomach.

A report from the patient, April 3, 1940, stated that she had gained 14 pounds, felt quite well and had had no more hemorrhages.

**Case 7.**—Hosp. No. 310-1: A female, age 45, was seen at the clinic, December 20, 1939, because of persistent anemia and weakness which had been present for two years. Her hemoglobin was 44 per cent, with an erythrocyte count of 3,340,000. Roentgenologic examination revealed a discrete, oval, pedunculated mass lying within the midportion of the antrum. At operation, December 30, 1939, a mass 3 cm. in diameter was found within the lumen of the stomach, attached by a broad base, which was considerably indurated. Subtotal gastrectomy was performed. The pathologic report was leiomyosarcoma. She was discharged, January 18, 1940, eating well and wound well healed.

This patient remains well but the operation is so recent that any follow-up report is without value.

In the light of our experience with sarcomatous degeneration in these tumors we do not believe that they should be treated by local removal but rather by high subtotal gastrectomy in order that the tumor and its base, together with a wide margin of gastric wall about it, may be included in the

removal. This procedure was employed in six of our seven cases. In the seventh case a large intragastric leiomyosarcoma the size of a grapefruit and attached by a moderate-sized base was removed by Dr. Samuel F. Marshall



FIG. 20.—Case 7: Roentgenogram of the stomach showing tumor of the antrum.

intragastrically, together with the attached section of the stomach wall, and the remaining defect in the stomach wall closed, the patient making an excellent recovery. This was done after Doctor Marshall and I had examined the stomach with the abdomen opened and arrived at the conclusion that because of the size of the tumor one would have to accept either intragastric removal together with the portion of the stomach wall to which it was attached or a total gastrectomy. Since the tumor was completely encapsulated and movable on its base, and since we did not know whether or not it was

malignant, the conservative procedure of local intragastric removal was chosen.

The type of malignant degeneration occurring in these tumors is usually of low grade and for that reason, even in the patients with the multiple leiomyosarcomatous lesions involving the entire stomach as shown in Figure 5 of Case 2, total gastrectomy is distinctly justifiable. This patient, whose photograph is shown in Figure 4, three and one-half years after total gastrectomy for a leiomyosarcoma involving the entire stomach (Fig. 6a), is able to eat nearly everything, to maintain her weight and, with the aid of

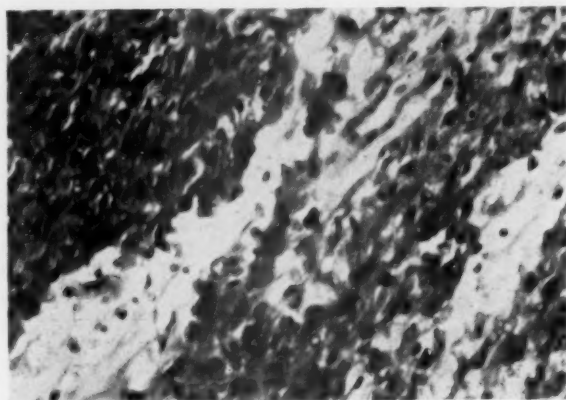


FIG. 21.—Case 7: Photomicrograph of portion of leiomyosarcoma showing marked edema of stroma, separating strands of atypical smooth muscle cells. ( $\times 300$ )

liver, hydrochloric acid and iron, to maintain her hemoglobin and red count at a normal level. In an experience with complete gastrectomy, now amounting to 27 cases, there have been but seven deaths. Sixteen consecutive total gastrectomies have now been performed with but three deaths. It has, therefore, been demonstrated that the operation has been developed technically to a point where its mortality rate, when one considers the magnitude of the procedure, is justifiable. It has been demonstrated that these patients with no stomachs, and a loop of jejunum serving as a substitute for one, can maintain themselves adequately as to health, activity, body weight and blood picture. Time and further experience will determine the position of this operation for advanced carcinoma of the stomach. Its applicability, however, in sarcoma involving the entire stomach seems at its best since there exists in these cases, particularly those of the leiomyosarcomatous type, even a possible prospect of cure in some of the cases showing low grades of malignancy.

#### CONCLUSIONS

- (1) Gastric leiomyomata are by no means uncommon.
- (2) They are frequently associated with hemorrhage, occasionally with pyloric obstruction and, not infrequently, sarcomatous degeneration.

In any patient with hematemesis or melena the possibility of this lesion should be kept in mind. Because of the possibility of sarcomatous degeneration, the tumor should be removed by wide subtotal gastrectomy and even in the advanced lesions, involving the entire stomach, total gastrectomy may still be applicable and justifiable.

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## CONGENITAL PYLORIC STENOSIS\*

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THE CAUSE of congenital pyloric stenosis is not known, although there are several theories. Fraser<sup>1</sup> subscribes to Thomson's<sup>2</sup> theory of the tumor being due to overaction of the stomach musculature and hence hypertrophy of the pylorus. Hurst<sup>3</sup> says: "It is clear that the obstruction is due to something which produces a much more powerful resistance than the simple absence of relaxation (achalasia). The only explanation is spasm." He believes "it possible that the tendency to spasm of the pylorus is the expression in an extremely exaggerated form of the constitutional condition called hyperthenic gastric diathesis, which manifests itself by hypertonus, hyperperistalsis and hyperchlorhydria, and occurs much more commonly in men than in women. The diathesis is often present in several members of a family—this would explain the rare instances in which two and even three or four members of the same family have hypertrophic pyloric stenosis." As opposed to Hurst's theory of hyperthenic gastric diathesis and those theories which deal with the basis of its being in a hypertonic child, one has the subsequent history of the cases that are cured by operation. My knowledge of the after-results is only of those cured by operative measures, and the subsequent history of these cases is that of a normal individual. In no case that we have been able to trace in our series has there been any subsequent history of digestive disturbance that would suggest a disability such as duodenal or gastric ulcer, or other disease which may be associated with hypertonicity. Strachauer,<sup>4</sup> and others, describe the lesion as having been found in a seven-month fetus and in a stillborn child. Cockayne<sup>5</sup> believes the condition has a genetic basis, though the way it is inherited is still uncertain and an environmental factor may be necessary for its production in addition to a generic one. The early age at which a well-marked tumor has been found, clinically and at operation, eight days in a case of this series, weighs heavily in favor of the condition being present before and at the time of birth; and this would seem to point to the genetic influence. Added facts, such as more than one case in a family (in our series five siblings apart from twins), speak strongly for the genetic etiology.

It is a condition that is most frequently found in the first-born of a family. In this series 51.8 per cent were first-born. This agrees with statistics published by other authors, but it seems to be a high percentage and challenges a rational explanation. The percentage of first-born children in the total number of births is greater in urban communities, where families are small. Yet even in such centers first-borns predominate (Table I).

There is reason to believe that more males are conceived than females,

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\* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

TABLE I

Order of Birth	Cases of Pyloric Stenosis		Average Births, Toronto	
	Number	Per Cent	Number	Per Cent
1st	144	51.8	4,748	41.2
2nd	61	21.9	2,730	23.8
3rd	41	14.7	1,627	14.1
4th	16	5.8	916	8.0
5th and over	16	5.8	1,476	12.9
Total	278	100.0	11,497	100.0

since a study of early miscarriages shows the percentage of males very high until figures at the time of birth show a slight preponderance only of males. Males are, therefore, less robust than females and have a poorer chance of surviving.

Twins, or a sibling twin, may have the condition. Sheldon<sup>6</sup> states that in 1,000 cases of congenital pyloric stenosis, 1-43.4 cases is a twin sibling, while the ordinary 1,000 birth-ratio is 1-80 births. In our series, one case in 36.3 cases is a twin, while the ordinary ratio for Canada is 1-83.4.<sup>7</sup> Cockayne<sup>5</sup> describes two pairs of twins who were first cousins; all four were proved to have congenital pyloric stenosis at operation. The occurrence of the condition in monozyotic or maternal twins is almost positive proof of a genetic factor being the producer of the condition. In the cases recorded,

TABLE II

## SUMMARY OF 12 CASES OF TWINS WITH PYLORIC STENOSIS

*Hospital for Sick Children, Toronto*

Year	Initials of Twins	Sex of Twins	Type of Twinning
1914-1915	R. R. ....	♂* ♀	Fraternal
1917-1918	R. McG. ....	♀* ♂	Fraternal
1925-1926	B. M. .... (Twin died. Parents describe the twins as identical, December, 1939)	♂* ♂	Doubtful
	A. G. ....	♂* ♀	Fraternal
1927-1928	Harvey and Grant I. .... (Reexamined November, 1939)	♂* ♂	Fraternal
1930-1931	Ross and Donald McF. .... (Reexamined December, 1939)	♂* ♂	Fraternal
1933-1934	R. W. ....	♂* ♀	Fraternal
1935-1936	William and Harry L. .... (Reexamined December, 1939)	♂* ♂	Fraternal
1937-1938	P. W. ....	♂* ♀	Fraternal
1938-1939	Garry and Glen T. .... (Examined 1938)	♂* ♂*	Identical
	Robert and Richard G. .... (Examined 1938)	♂* ♂*	Identical
	Erla and Arla C. .... (Examined 1939)	♀* ♀	Fraternal

\* The symbol \* indicates the condition.

# CONGENITAL PYLORIC STENOSIS

there are many reports of pairs of twins each having the condition, but few have been studied sufficiently to prove the type of twinning present.<sup>7</sup> There seems to be a reasonable doubt that identical twins are not both affected when the condition is found in one. In our series, there were 12 pairs of twins, two pairs being identical twins. All four had a tumor, proved at operation. In all fraternal twins, one sibling only was affected (Table II). Multiple births are known to produce a disturbance of growth, and this may prove to be an environmental factor influencing the hypertrophy of the pylorus.

This series includes all cases of congenital pyloric stenosis reaching the Hospital for Sick Children. There were 28 cases which had no operative treatment, some being diagnosed only at autopsy, and who had received treatment for some other condition. Of those cases treated without operation, ten were discharged as improved and 18 died. Of these cases dying, the cause of death is given as bronchopneumonia, otitis media and septicemia, marasmus and acute intoxication. Of the cases submitted to operation, *viz.*, 402, 52 died subsequently from intoxication, malnutrition, decomposition, otitis media

TABLE III  
CASES BY YEARS

	No. of Operations	Cured	Died	Not Operated Upon	Cured	Died
1914.....	2	2				
1915.....	1		1	1	1	
1916.....	3	2	1	3	3	
1917.....	7	5	2	2	1	1
1918.....	11	8	3	11	5	6
1919.....	9	8	1			
1920.....	6	4	2			
1921.....	15	10	5			
1922.....	15	12	3	1		1
1923.....	12	11	1	1		1
1924.....	27	22	5			
1925.....	14	12	2			
1926.....	31	24	7			
1927.....	15	10	5	1		1
1928.....	25	24	1	1		1
1929.....	30	28	2	1		1
1930.....	14	12	2	2		2
1931.....	20	19	1	1		1
1932.....	22	18	4	1		1
1933.....	14	14		1		1
1934.....	9	7	2	1		1
1935.....	19	19				
1936.....	10	10				
1937.....	12	12				
1938.....	23	21	2			
1939.....	36	36				
Totals.....	402	350	52	28	10	18

and general infection, and in a few cases, there was a peritonitis due directly to the opening of the duodenal mucous membrane (Table III and IV).

TABLE IV

## CONGENITAL PYLORIC STENOSIS

*Hospital for Sick Children, Toronto—430 Cases*

Males 352—81.9%      Females 78—18.1%

Place in family not known—13. Others as below

1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
213	84	61	31	14	6	5	2	1	1
51.1%	20.1	14.6	7.4	3.3	1.4	1.2	0.47	0.24	0.24
Treated by Operation					Died		Mortality		
1914-1923 incl.				81	19		24.4%		
1924-1933				212	29		13.0%		
1934-1939				109	4		3.6%		
1914-1939				402	52		12.9%		
Not operated upon				28	18		64.3%		

The symptoms of pyloric stenosis are occasionally found within a few hours after birth. Vomiting has been known to have occurred as early as this and to have continued through until the condition was cured. Of the symptoms that are present in the disease, vomiting will be found to be one of the most outstanding. It is of a special character. Inasmuch as it is the result of a pyloric obstruction, it will be large in quantity and be free of bile discoloration. Loss of weight, which occurs in the normal infant for two or three days after its birth, will be found to continue on until, at three weeks, the infant may be less in weight than at the time of its birth. In spite of the vomiting and the loss of weight, the patient will be found to have a splendid appetite. It takes its nourishment with avidity. The stool is found to be bile-stained, but may be small and scanty and bearing some relation to the amount of food that gets through the pylorus. The infant is dehydrated, its skin is shrunken, and it has very little subcutaneous fat. It is fretful and cries a great deal. Examination of the abdomen shows the abdomen scaphoid with visible peristalsis to be seen to sweep from left to right, gaining in size and activity with the increased amount of food taken into the stomach. When a fastigium has been reached an explosive vomiting occurs which partially empties the stomach. The vomiting is characteristic in that the propulsion is such as to throw the vomitus a considerable distance from the lips of the infant. A stream may be shot out as far as 18 inches. It comes out through the nasopharynx and nostrils. On palpation of the abdomen, it is possible to feel an enlargement in the pyloric region. The tumor is to be felt by examination of the hypergastric region on the right side. Digital examination, just below the level of the costal margin and just lateral to the edge of the rectus, may palpate a hard nodule about the size of a large hickory nut. This nodule is movable and is more easily felt when

## CONGENITAL PYLORIC STENOSIS

the peristaltic wave in the stomach has lifted up the pyloric nodule to a position where it is more superficial.

Blood and urinary tests have no characteristic changes of diagnostic value.

The diagnosis of this condition should be relatively simple. The history of loss of weight, vomiting, visible peristalsis, in an infant, is to be considered as a probable case of pyloric stenosis. The earliest case that has been operated upon by the writer was one eight days of age. It was found to have a well-marked and definite tumor. The symptoms may not appear until two or three weeks after birth and then a history is given of a sudden onset. At operation, a well-marked tumor may be found, which makes it difficult to explain why there should have been no obvious symptoms before the sudden onset.

In the diagnosis of a case of pyloric stenosis the examiner should, in suspected cases, have the patient stripped of all clothing, lying on its back, with a good light on the abdomen. The infant should be given some sweet water or glucose solution in a nursing bottle, and, as it nurses, the upper part of the abdomen should be observed. As the patient fills his stomach the epigastric region will be seen to fill out, and, presently, waves of peristalsis will be observed to originate in the left side of the abdomen and sweep across to the right. With an increasing volume entering the stomach the waves will be seen to increase in magnitude and speed. When they become very pronounced the patient is seen to stop nursing, draw its legs up and cry, and eventually when the waves have become of great magnitude, explosive vomiting occurs. The stomach being emptied of the larger part of its contents, the child will immediately again take the bottle in an endeavor to get some nourishment. It is an opportune time to palpate the right hypocostal region to examine for the presence of the pyloric tumor. The left hand lifting in the right flank of the patient assists the second finger of the right hand to identify the tumor in the epigastrium. An examination which has demonstrated visible peristalsis with projectile vomiting and the identification by palpation of a pyloric tumor may be considered as sufficient for diagnosis of an obstructive congenital pyloric lesion. A thin barium mixture may be given in order to obtain roentgenographic verification, but this type of examination is not to be encouraged as there is a certain danger associated with the giving of barium to an infant who has pyloric stenosis. The liability of the barium producing an acute obstruction in the very narrow lumen of the pylorus is a real danger. A proper physical examination of the infant will give all the needed information to enable one to make an accurate diagnosis.

The condition is best treated by operation. It has been claimed that the condition is amenable to well-supervised medical treatment. Yet such treatment, when successful, is prolonged and difficult, demanding the utmost in the parents' devotion in the care of a crying infant over many months. Whereas operative interference relieves the obstruction of the pylorus im-



mediately, and one may expect the function of the stomach to be immediately restored in large part or completely. This condition lends itself perfectly to surgical interference. It is surgery's best operative procedure. Any infant who has pyloric stenosis should be operated upon for the relief of the obstruction.

Steps must be taken to make it a good operative risk. The most important factor in the treatment of the infant is an early recognition of the condition. Surgery undertaken before there has been serious interference with the patient's health gives the best results, as is well demonstrated by the reports of Barrington Ward.<sup>8</sup> When the patient has been allowed to experience a starvation of sorts for weeks its general condition will be much affected. Dehydration will be present and it must be overcome by the administration, intravenously, of suitable fluids, such as normal saline, glucose 5 per cent, and blood. When acidosis is present whole blood transfusions are indicated. The infant can then be considered safe for operation. There are no contraindications for operation except the unfavorable condition of the infant, and this can generally be corrected by intravenous therapy in from 24 to 48 hours, to a degree that will permit the surgical procedure.

When operation is finally decided upon, the question of an anesthetic becomes of importance. In this series, almost all types of anesthetics have been tried. The experience of the writer is that ethyl chloride and ether, or ether without the ethyl chloride to initiate anesthesia, is much the best method. Local anesthesia has not proved satisfactory, as it is very difficult to restrain a struggling infant. Inasmuch as the operation is simple and can be performed in a very short period of time under favorable conditions, a general anesthetic is the best. It will be found most useful to have a small section of board about 24 inches long and six inches wide. This board is padded. The infant is laid upon this, with the legs bound to the board, somewhat in the manner of a papoose. This arrangement controls the infant, so that if it be not deeply anesthetized it cannot flex its thighs or move its legs. Before the anesthetic is begun a catheter should be introduced into the patient's stomach and the stomach contents withdrawn. The stomach having been emptied, the anesthetist may proceed with the administration of ether. Conforming to the size of the infant's face, a simple wire mask covered with ten thicknesses of gauze is used.

*Operative Procedure.*—The skin is prepared by washing with soap and water, drying, and then applying 2½ per cent iodine in 70 per cent alcohol. Standing on the right of the patient, an incision is made parallel to the right costal margin and about one-half inch below it. The inner extremity of this incision should be lateral to the edge of the rectus, and the incision need not be longer than 2½ inches. The skin and deep fascia having been divided, the external oblique is split in the direction of its fibers, the internal oblique is then identified and split in the direction of its fibers. The transversalis fascia and peritoneum are generally closely applied and can be divided as

## CONGENITAL PYLORIC STENOSIS

one. When this incision has been properly made through its entirety, the liver will be found to be exposed and will be blocking any attempt on the part of the abdominal parietes to extrude through the wound. A finger can then be passed around the edge of the liver and one can immediately identify the hard tumor of the pylorus. A pair of ring forceps without rubber or a pair of sponge forceps are then used to grasp the stomach, and by delivering part of this the pyloric tumor is, usually, easily drawn through the wound. It is sometimes found that the tumor is very large and the wound may have to be enlarged to permit the delivery of it outside the abdomen. The left thumb and forefinger then grasp the duodenum at the lower extremity of the tumor and squeezing the fingers together presses the lower part of the tumor presenting in the duodenum toward the stomach. The tumor will be found to have an avascular line on its superior border. This superior border is concave, the whole tumor having the appearance of a large cashew nut. A simple incision about half an inch long and just deep enough to allow the engaging of the closed tips of tendon scissors is all that is required. The closed points of these tendon scissors engaged in the wound are spread. The tumor will be found to split from end-to-end, and through its thickness, until the mucous membrane of the pylorus is seen appearing as a white and glistening structure in the bottom of the split. When the tension is taken off the scissors in the split tumor this mucous membrane will be found to bulge into the split. It is not necessary to divide every last strand of the tumor at its lower extremity, and it is courting danger to attempt it. All pyloric tumors project into the duodenum, as a cervix into the vagina. When one endeavors to split the extremity of the tumor at its duodenal end, he will almost invariably open the mucous membrane and have soiling of the wound from stomach content, in addition to hemorrhage coming from the torn membrane. When this event occurs it becomes necessary to suture this small opening as it has been known to produce peritonitis, which has ended fatally. The writer believes that the squeezing of the duodenal end of the tumor, in such a fashion that it is expressed towards the stomach, permits one, when the tumor is split with the scissors, to have it sufficiently divided for all practical purposes. When the tumor has been split in the avascular region, it will be found there is no hemorrhage occurring that requires any attention. The tumor is dropped back into the abdomen. No steps are taken to cover the split in the tumor by grafts or fat or strips of muscle. The lower edge of the liver slides back into position, and one can close the peritoneum and different muscle layers without interference of abdominal contents extruding through the wound. The writer uses No. 0 catgut to close the different layers, and No. 000 chromic catgut in the skin. The wound is dressed by applying a small gauze strip over bismuth-formic iodide powder. This dressing is slightly larger than the wound. Mastisol is applied, surrounding the wound, and a section of gauze bandage is placed over the dressing and pressed on to the drying mastisol and trimmed off, so that the

whole dressing is not more than two inches wide and three or four inches long.

Following the operation a transfusion of whole blood is administered when it is felt dehydration or shock requires it.

*Postoperative Feeding.*—One-half ounce of breast milk four hours after operation. Feeding increases one drachm every four hours until a total of 3 oz. q. 4 h. x 5 is given, unless the child vomits, in which case the amount of feeding remains the same without any increase at the end of the four-hour period. After the amount of the feeding has reached 3 oz. q. 4 h. x 5, it is changed back to the feeding given previous to operation, or started on 2 per cent L.A.M., 4-5 oz., q. 4 h. x 5.

We have found this treatment satisfactory and see no reason why we should change it. Recently, it has been suggested that no feeding be given for 24 hours following the operation. This is based on the observation that infants vomit during the first 24 hours when they have been fed, and that barium administered shortly after operation is not emptied promptly from the stomach. In spite of this suggestion we feel that the infant should be fed four hours after operation and that occasional vomiting should not interfere with the routine of feeding.

We have had the cooperation of the staff in pediatrics, in the care of these cases. The cases are admitted to their wards, and when operation is performed the pediatrician still directs the feeding and general care. Without this cooperation the problem would be very difficult for the surgeon.

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*DISCUSSION.*—DR. WILLIAM E. LADD (Boston, Mass.): There is no question but that the advance in treatment of congenital pyloric stenosis in the last 25 years has been one of the most striking improvements in the whole surgical field. I find this a difficult paper to discuss because the treatment has become so well standardized, because there are few controversial points, and because I can find little or nothing to disagree with in Doctor Robertson's paper.

#### RESULTS IN 765 CASES OF PYLORIC STENOSIS

Years (Inclusive)	Number of Cases	Deaths	Mortality Per Cent
1915-1922.....	125	15	10.4
1923-1928.....	150	11	7.0
1929-1931.....	151	3	2.0
1932-1935.....	162	8	4.9
1936-1939.....	177	1	0.56

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During the early part of the period, after we had adopted the present operation of pyloromyotomy, I believe our high mortality was largely due to having poor risk patients and to an inadequate knowledge of how to combat dehydration. Both of these handicaps have been largely overcome. The pediatrician now realizes that this condition is a surgical problem and refers the patient earlier, and our knowledge of fluid balance has been greatly improved. However, in spite of this situation, complications still arise which sometimes prove fatal.

In the earlier series, reported in the literature, some fatalities were reported from hemorrhage from the cut pylorus. This can be avoided by selecting, for the incision, the bloodless area on the superior surface of the pyloric sphincter. Cutting through the mucous membrane at the duodenal end of the pylorus is an error which it is easy to make. I think every member of my staff, including myself, has made this mistake once—but only once; and in no instance has a peritonitis resulted. This error is serious only if it is not recognized—then a fatality will probably follow.

Disruption of the wound has taken place several times in our series and in one instance caused a fatal peritonitis.

The several factors involved in this failure of wound healing are probably subclinical scurvy, low protein and edema, and technic of making and closing the incision. During the last two years we have given all these patients vitamin C before and after operation to overcome the first factor. We have probably paid too little attention to the question of low serum protein. We have varied our technic of wound closure. The last type of closure employed has consisted in medial retraction of the rectus muscle and closure by layers with silk supplemented by stay sutures to, but not through the peritoneum. Doctor Robertson's suggestion of a gridiron incision under the costal border and outside the rectus muscles has many obvious advantages and I plan to adopt it at the next opportunity.

The suggestion recently raised by Faber and Davis, of San Francisco, that feeding be withheld for a period of 24 hours, or more, does not appeal to me as being sound. Our present feeding regimen which is similar to Doctor Robertson's has proved eminently satisfactory.

DR. ALBERT O. SINGLETON (Galveston, Tex.): I wish to discuss one phase of the problem of pyloric stenosis which Doctor Robertson has so ably presented, and this has to do with the incision which is employed.

The accompanying illustration (Fig. 1) illustrates the type of incision we have found very advantageous. It is made quite far to the right, since the pylorus in infants will be found much further to the right of the midline than in adults. With the posterior sheath of the rectus split in a transverse direction, sufficient room is obtained. With the pylorus delivered into the wound, there is no room for the evisceration of the small intestine and omentum, which may happen in these infants with their tremendous intra-abdominal pressure. This is particularly noticeable under local anesthesia which we are in the habit of using. Also, postoperative disruption cannot occur. Doctor Robinson's suggestion of making the incision still further to the right, even outside of the rectus muscle, may be a very good one.

DR. EDWARD J. DONOVAN (New York, N. Y.): I was very much interested in Doctor Robertson's paper on pyloric stenosis, since he has brought out a great many facts, particularly in regard to the twins, that I have not heard discussed in relation to pyloric stenosis before. We have had no identical twins in our series, and my experience with this condition consists

of about 425 cases that I have operated upon personally. Our cases have followed those of Doctor Robertson very closely. We have found that the condition occurs about five to seven times more often in boys than in girls, that is, there are between 14 and 18 girls in each 100 cases. All nationalities are represented, and in a city where there is a large colored population there are about two colored children in each 100 cases.

We do not know any more about the etiology than anyone else, but have felt, because we have had several cases in premature infants with pyloric tumors that were very easily palpable, that the tumor was congenital in origin, and an associated pylorospasm caused the onset of symptoms between the

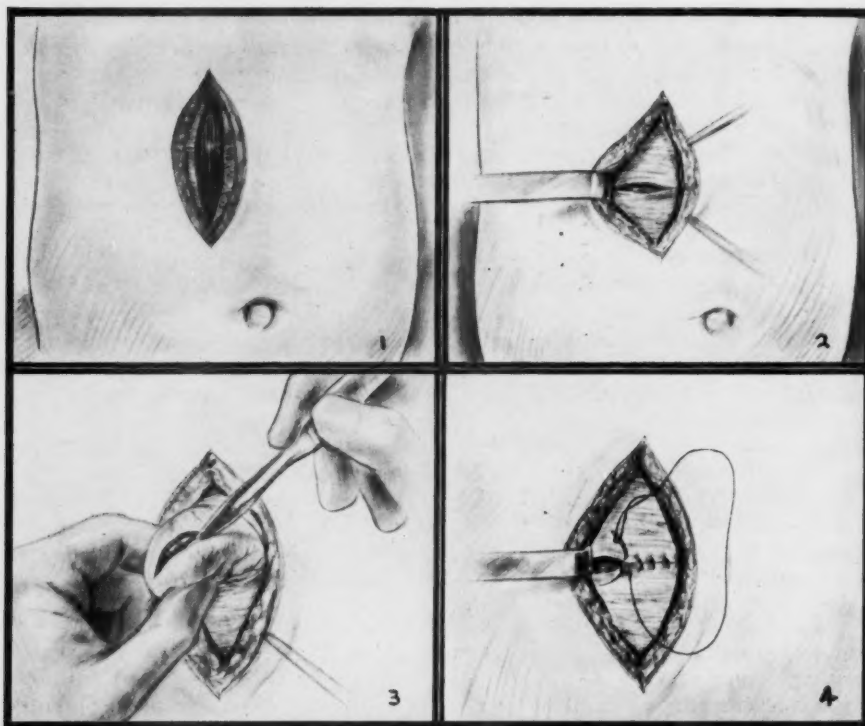


FIG. 1.—Drawings showing (1) the position of the incision employed; (2) the approach to and (3) the delivery of the pyloric hypertrophy; and (4) the method of closure of the wound.

second and fifth weeks. We employ the Fredet-Rammstedt operation with a very high right rectus incision and retract the right lobe of the liver upwards in order to reach the pylorus. I think Doctor Robertson's incision may be better than the right rectus because we have occasionally found that it is difficult to deliver the pyloric tumor through this high right rectus incision. I will try some cases using Doctor Robertson's incision.

The operation that we perform is exactly the same as that done by Doctor Robertson except that we use a curved mosquito clamp to spread the muscle surfaces instead of scissors.

We believe in feeding these babies very promptly after operation. We give them 15 cc. of water two hours after operation, and their first feeding, which consists of breast milk and barley water, three hours after operation.



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Very few of these babies vomit after operation, if you empty the stomach completely in the operating room.

We use ether in all cases and pass a stomach tube and completely empty the stomach before we make the abdominal incision.

We have concentrated most of our attention on bringing the mortality down. When I started my series we were still operating upon them as emergencies. I remember very well going down to the Babies' Hospital one Sunday afternoon and operating upon one who had been sent in by a pediatrician, and the indication for operation in those days was that the baby was vomiting everything. No one seemed to give any thought as to whether the baby was able to stand such an operation or not. We have, in recent years, concentrated a great deal of our attention on the preoperative preparation, particularly the restoration of the fluid balance, and feel that the amount of vomiting is unimportant. Sometimes it takes between four and five days to prepare these babies for operation. In 1931, I reported my first 100 cases with one death and have had no deaths since then. In 1935, I reported 243 cases with the same one death. Last year, I reported 350 with the same death, and since that report I have had about 60 more and have lost none.

DR. EDWIN M. MILLER (Chicago, Ill.): I hesitate to discuss a paper presented by one who has had a much wider experience than I in this field. During the past 20-odd years my experience has been limited to about 40 Rammstedt operations. My object in discussing this paper is to say that I feel one seldom has an opportunity to grossly and microscopically examine the pylorus of an infant upon whom this operation has been performed some time previously. This opportunity has come to me recently in a case that I operated upon in September, 1939—an infant, at that time two months old, weighing less than birth weight, presenting a typical picture in all respects with a definitely palpable pyloric tumor.

Last month this infant died of some cerebral disturbance, and they found in the records that I had operated upon the baby six months previously. They were kind enough, therefore, to turn the specimen over to me for examination.

I made a photograph, which was not a very good one, showing the duodenal mucosa and the anterior surface of the pylorus. I was surprised to find, on pathologic examination, how smooth this area was and the very little scar in this region. Transverse sections were made through the central portion of the pylorus, and the gross appearance across the center of the pylorus, apparently, differs somewhat, I would say, from the conception as illustrated in one of Doctor Robertson's photographs. Microscopically, it is difficult to decide where the incision had been made; that is, it was difficult for our pathologist to decide. He could not positively say, after thoroughly looking at this section a few days ago, where the incision had been made, but because of the thinner area in one quadrant I imagine that is the point where the operation had been performed.

DR. WARREN H. COLE (Chicago, Ill.): Apparently we all agree that one of the most important features in bringing the mortality rate down in this disease lies in the fact that we are paying more attention to the electrolytic and fluid balance and bringing them up to normal before submitting these patients to operation. As some of the discussers have already mentioned, it is important to evacuate the stomach before the child is sent to the operating room. This will help the anesthesia and, certainly, will lead to a

smoother postoperative course; it may be necessary to evacuate the stomach again at the end of the operation if the child has swallowed a great deal of air.

It is likewise agreed that either general or local anesthesia may be used. I prefer local, and if, preoperatively, a mild sedative, such as second or nembutal is given, the local anesthetic will behave much better. I have never seen any ill effects from mild sedation of this style.

A second very important feature in the progress of the child postoperatively lies in the question as to how well the feedings are retained. I am quite convinced we can control this phase of convalescence to a large extent by watching the amount of feedings. I heartily agree that we should start feeding these children a few hours after operation, and should increase the amount rapidly up to about a normal feeding. However, if vomiting becomes significant during the course of the first few days, feedings should be reduced immediately to one-half the original amount, and increased gradually. In my experience this will almost invariably stop the vomiting. We will certainly grant that if over a given period of time a child took ten ounces of food and vomited eight, the situation would be much worse than taking five and vomiting none.

I should like to heartily endorse Doctor Ladd's statement about the use of vitamin C. I think this phase of therapy is tremendously important, and when you add closure of the wound with silk to that precaution, the incidence of wound disruption will be reduced practically to zero.

I wish to call attention to a final, and not insignificant point, namely, that a good spirit of cooperation with the pediatrician must be attained lest he attempt to treat these infants too long medically.

DR. WALTER ESTELL LEE (Philadelphia, Pa.): It would seem that nothing could be added to this discussion of the subject of congenital pyloric stenosis because everyone at the present time seems to be in agreement. I would like to express my personal appreciation of the suggestion of Doctor Robertson that a gridiron incision should be made in the subcostal region to the right of the semilunar line. I too have found, as Doctor Ladd has said, that the muscle-splitting incision is usually too far medially to be ideal.

May I suggest the addition of two procedures to the technic: For some ten years, we have operated entirely under local anesthesia. After the preliminary administration of luminal or nembutal, we give the child, shortly before operation, a sugar teat to suck. You may be surprised to hear that in the Quaker City the so-called sugar teat is made up of ten drops of paregoric and ten drops of whiskey or brandy to one ounce of a 5 per cent glucose solution. You will, likewise, be surprised how the babies take to this mixture, and also, more or less, amused by how promptly they become happily intoxicated.

The other suggestion has resulted from the observations of one of my assistants, Doctor Summey. In the past, one of our greatest difficulties, and most embarrassing complications, has been the failure to obtain primary union of the celiotomy wound in but a small proportion of cases. This involves merely the skin and the subcutaneous tissues, not the muscle sheaths, and we have not as yet had a wound disruption. After the removal of the skin sutures these infections promptly heal and we have had no herniae develop. Doctor Summey had been experimenting independently; and I was, eventually, informed by the nurse that they never had a breakdown in their wounds, as I did in mine! The explanation, apparently, is due to the fact that they have been using through-and-through, unabsorbable mass sutures

# CONGENITAL PYLORIC STENOSIS

which pass through skin, subcutaneous tissues, muscle and peritoneum, and which are then tied over rolls of gauze after the skin edges have been approximated by interrupted mattress sutures of silk. Since employing this technic I have had primary union in every case. This, of course, is in line with Doctor Lahey's contention that in the closure of celiotomy wounds it is not necessary to employ layer sutures, and that through-and-through sutures of nonabsorbable material, down to the peritoneum, result in the lowest incidence of wound complications. It seems reasonable that the tissues in infants may not be capable of handling too much foreign body in the form of suture material.

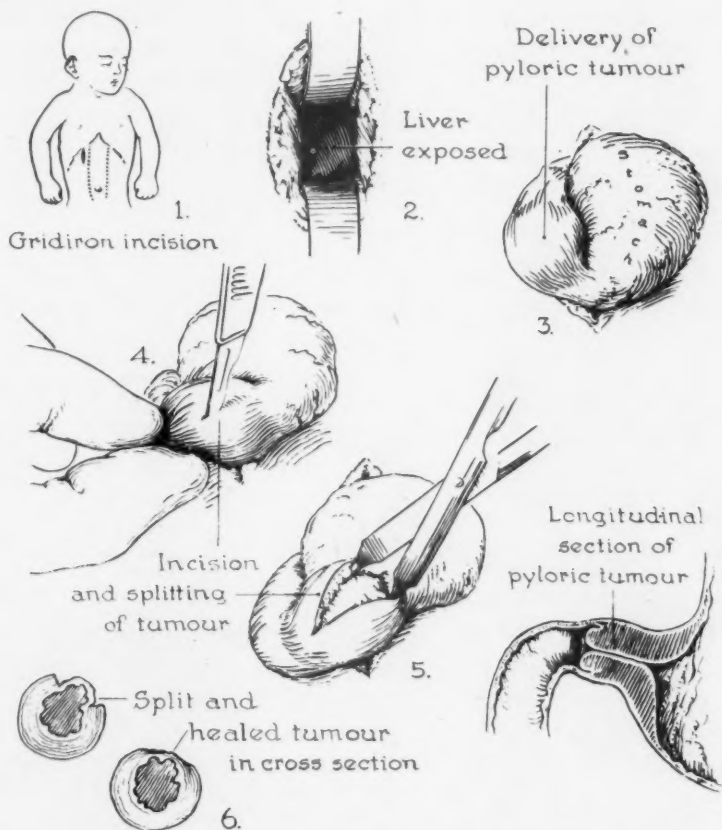


FIG. 1.

DR. D. E. ROBERTSON (Toronto, Canada, closing): It may be of interest to demonstrate by a drawing the gross specimen from a child who died of pneumonia three or four months after operation, which is a true representation of the condition present in the stomach (Fig. 1). In the pathologic specimen, just a thin layer of fibrous tissue covering the mucous membrane is to be seen. It is quite smooth externally and there is no muscle layer to be found.

In regard to the incision, I do believe that the best incision is the gridiron incision which can be closed by layers, and I think one should use No. 0 chromic catgut. I use No. 000 chromic catgut in the skin. Chromic catgut is used as I believe it is less irritating than plain catgut. When a sterile dressing is applied over the wound, with mastisol to hold it on, the wound need not be disturbed for ten days to two weeks.

## ABDOMINAL NEOPLASMS OF NEUROGENIC ORIGIN\*

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THE NEUROGENIC TUMORS of the abdomen present many diversified and interesting features, both from the clinical and pathologic aspects. The purpose of this paper is a consideration of the clinical and pathologic features of 18 nerve sheath tumors and an attempt at their correlation. The neuroblastic tumors of the sympathetic and chromaffin systems were purposely excluded from this report (Table I).

TABLE I

### ABDOMINAL NEOPLASMS OF NEUROGENIC ORIGIN

#### I. Nerve Sheath Tumors

##### A. Benign

1. Neurolemmoma (schwannoma—perineurial fibroblastoma)
2. Neurofibroma (of type associated with von Recklinghausen's disease)
3. Cirroid or plexiform neurofibroma
4. Ganglionated neurofibroma

##### B. Malignant

1. Neurogenic sarcoma

#### II. Neuroblastic Tumors of Sympathetic System

1. Sympathoblastoma
2. Paraganglioma
3. Ganglioneuroma

*Embryology and Anatomy.*—To understand the histogenesis of the nerve sheath tumor, a brief review of the embryology and anatomy is essential. These tumors arise from the abdominal autonomic nervous system.

A peripheral nerve consists of an axis cylinder (neurite) which may or may not be invested by a medullary sheath (myelin) which is a product of the neurite. The next layer is the neurolemma, or what is commonly known as the sheath of Schwann. This is of neuro-ectodermal origin and is composed of a syncytium of Schwann cells. The third sheath is known as the sheath of Henle (or endoneurium) which is fibroblastic in character and consequently of mesodermal origin. This constitutes a single nerve fiber. Bundles of nerve fibers constitute fasciculi, and these are surrounded by a connective tissue layer known as the perineurium. About the entire nerve with its component fasciculi is a third connective tissue sheath, known as the epineurium.

The neurite arises from the medullary crests. The sheath of Schwann also has been shown, by ingenious and meticulous experiments by Harri-

\* Read before the American Surgical Association, St. Louis, Mo., May 2, 1940.

son,<sup>1, 2</sup> to be neuro-ectodermal in character and to be derived from the ganglionic crests.

Virchow, in 1863, divided the tumors of the periperal nerves into two groups, the false neuromas and the true neuromas. The true neuromas were those composed of nerve fibers or nerve cells, while the false neuromas arose from the nerve sheaths. According to the present day conception, the only true neuromas are those arising from the primordial cells of the sympathetic and chromaffin systems and are neuroblastic in character, while the false neuromas are composed of a combination of sheath cells (Schwann cells) and a varying degree of fibroblastic tissue.

In reviewing the literature, one will find that there is no uniformity of opinion as to the histogenesis of nerve sheath tumors. Verocay,<sup>3</sup> Masson,<sup>4</sup> and Antoni<sup>5</sup> feel that these tumors arise from the sheath of Schwann, and thus are of neuro-ectodermal origin. Mallory<sup>6</sup> and Penfield<sup>7, 8, 9</sup> believe that they arise from the connective tissue sheath of Henle, and thus are of mesodermal origin. Other observers believe, as we do, that in the present state of our knowledge, one cannot state with certainty the exact site of origin, for both types of tissue are said to form similar intercellular substances and to have the same histologic architecture. Special staining methods are still not specific enough to differentiate between these tissues to decide this problem. We do feel, however, that certain of the nerve sheath tumors, which we have designated "neurolemmomas," are composed primarily of Schwann cells, while there are others, such as the neurofibromas, that are composed of both Schwann cells and fibrous tissue. These latter tumors are usually found associated with a generalized neurofibromatosis (von Recklinghausen's disease). The neurogenic tumors of the abdomen are usually solitary and not associated with either multiple abdominal or cutaneous tumors. However, as Stout<sup>10, 11</sup> comments, unless one is particularly interested in this problem, the stigmata of von Recklinghausen's disease are often overlooked. In only two of our 18 cases was there evidence of such a constitutional disorder.

The benign nerve sheath tumors are of four types: (1) The neurolemmomas (schwannomas, or perineurial fibroblastomas); (2) the cirroid or plexiform neurofibromas; (3) the neurofibromas of the type associated with a generalized neurofibromatosis; and (4) the ganglionated neurofibromas.

The *criteria* for the diagnosis of the neurogenic tumors were based upon the presence of specific histopathologic features characteristic of these tumors as demonstrated by special staining methods. Each neoplasm was thoroughly studied by special differential stains known to be of the utmost value in differentiating these tumors from other neoplastic lesions within the abdomen. The stains used were hematoxylin and eosin, Masson's trichrome, Mallory's phosphotungstic acid hematoxylin, and Perdrau's method for silver impregnation of reticulin. In Masson's trichrome stain, the Schwann cells stain pink and have pink protoplasmic end processes which anastomose with similar



end processes of the neighboring cells to form a syncytium. These end processes are encased in a sheath of greenish-blue staining collagenous-like material. The large wavy collagen fibers stain a deeper greenish-blue. Mallory's phosphotungstic acid hematoxylin stain stains the Schwann cell a pinkish-brown and the nucleus blue. The reticulin about the cells appears a yellowish-brown and the larger wavy collagen fibers are orange-brown. Perdrau's method of silver impregnation stains the reticulin black and gray-black while the collagen fibers appear violaceous.

*Neurolemmomas.*—The abdominal neurolemmomas are confined largely to the stomach and retroperitoneal regions. While they are rare in the abdomen, they have been reported more frequently in the thorax, neck, trunk, and extremities. Furthermore, they are not necessarily solitary neoplasms for they may be associated with von Recklinghausen's disease. These tumors were



FIG. 1.—Case 3, L. P.: Actual size section of a gastric neurogenic sarcoma (Fig. 11 A) showing its origin in the submucosa, the deep penetrating ulcer, and the whorled cut surface.

first described by Verocay, in 1910, and called by him neurinomas. In the gastro-intestinal tract, they arise from the sheaths of the sympathetic fibers of the submucosal and myenteric plexuses. They are reported as having a predilection for the myenteric plexus of Auerbach, but of five gastric cases in which this could be determined, two can be definitely shown to arise in the submucosa as shown in Figure 1, and three in the subserosa. Of the three intestinal cases, two arose in the submucosa, and one in the intermyenteric region. Definite attachment to nerves, however, was impossible to demonstrate.

*Gross Characteristics of Neurolemmomas.*—Neurolemmomas are usually well encapsulated, slowly expanding neoplasms. They may be either solid, or cystic—usually the former. In only one of our cases was there marked cystic formation, as will be described later. There may be numerous small areas of cystic degeneration of small caliber throughout the tumor which may give it a spongy consistency. These tumors are usually of moderately firm consistency, being less firm than a carcinoma or pure fibroma. The

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contour is oval, or round, and frequently nodular. The cut surface often has a whorled appearance and ranges from a gray to a grayish-yellow or grayish-pink color with scattered hemorrhagic areas appearing red. The yellow

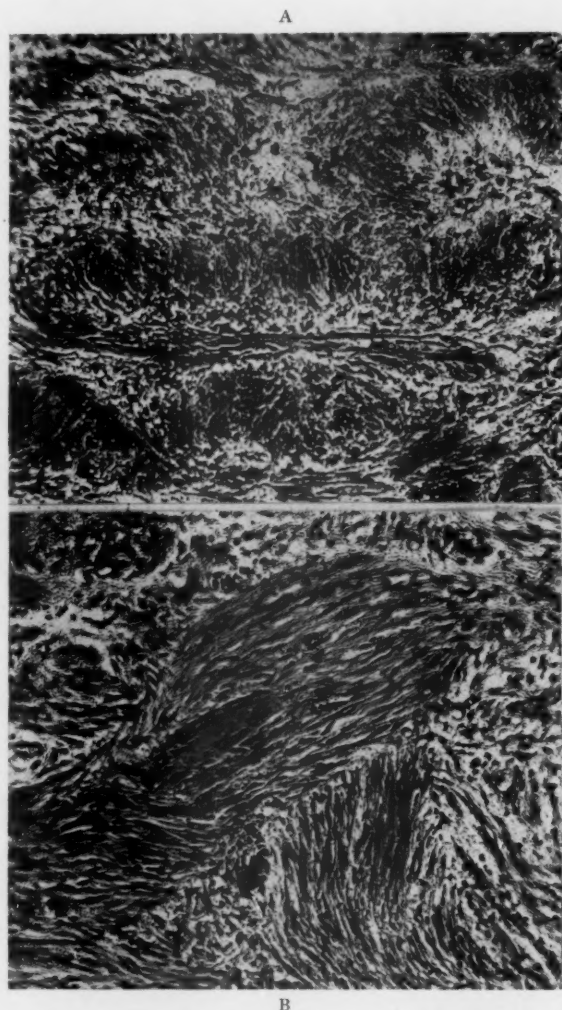


FIG. 2 A.—Case 2, R. B.: Photomicrograph of a gastric neurolemmoma (Fig. 10 A) showing marked palisade formation (Antoni Type A tissue). (H and E stain)

B.—Case 8, G. K.: Photomicrograph of a neurolemmoma of the gastrocolic ligament (Fig. 14 A) showing interlacing bands, whorls, and palisade formation. (Mallory's phosphotungstic acid hematoxylin stain)

areas are the result of necrosis. The tumors composed of Antoni's Type B reticular tissue are said (Geschickter<sup>12</sup>) to be larger in size when first recognized, gelatinous in consistency and to present a translucent gray-appearing cut surface. A characteristic gross feature of the gastric neurolemmomas is the deep-seated ulcerations of the mucous membrane surface.

*Histopathology of Neurolemmomas.*—For the histopathology of neurolemmomas (Schwannomas, perineurial fibroblastomas) we are indebted to the painstaking researches of Masson, Verocay, Antoni, Mallory and Penfield. There are certain definite characteristics that identify them as neurolemmomas. Antoni states that they are composed of two types of tissue, which are known as Antoni Type A tissue and Antoni Type B tissue. Rarely is a neurolemmoma composed entirely of one type of tissue to the exclusion of the other. One type usually predominates, but both types may be found in varying quantities. The Type A tissue is orderly in character, consisting of palisaded rows (Fig. 2 A) of slender elongated cells with blunt ends which give rise to long, thin, anastomosing protoplasmic end processes which anastomose with similar ramifications from neighboring cells to form a syncytium. These anastomosing end processes are covered by a thin layer of collagenous-like material. Throughout the tumor are seen large wavy collagen fibers. The nuclei are narrow, elongated, hyperchromatic and appear to be of an adult type. The important feature of this type is the palisade formation in which the cell nuclei lie parallel to each other. There is also a characteristic whorl formation of interlacing cords of cells (Fig. 2 B) which differ from the whorls seen in fibromas. Masson accounts for the palisaded effect by Schwann cell proliferation in a longitudinal manner within the endoneurium. The palisading may not be found in all neurolemmomas. There may be present only whorling, interlacing bands and reticular type of tissue (Antoni Type B tissue). The tumors least likely to become malignant are those showing the most striking palisade arrangement.

Antoni's Type B reticular tissue is a loose meshed somewhat edematous or myxomatous appearing tissue without differentiation or orientation of the fibers (Fig. 3). Antoni believed that there was a jellification and swelling of the collagenous fibrils and sheaths. This supposedly results in a separation of the tumor cells without interrupting their anastomoses to give a reticular architecture which takes the silver stain as shown in Figure 4. This belief is similar to that of Masson who contends that the reticular type of tissue results from degeneration.

*Plexiform or Cirroid Neurofibromas.*—Plexiform neurofibromas appear to be a manifestation of a more constitutional disease. There were no examples of this type in our series. One of our patients who had neurofibromas of the jejunum also had an extensive plexiform neurofibromatous involvement of the pelvis, prostate, periprosthetic tissues, scrotum, left buttocks, and thigh. The plexiform neurofibromas result from an overgrowth of both the fibrous and schwannian elements of the nerve sheath within the perineurium, so that there is a large, tortuous, twisted, matted tumor mass attached to and often extending along the course of a nerve. This condition is known as elephantiasis nervorum. In none of these cases, even by the use of special stains, has it been possible to detect an actual proliferation of the nerve fiber (neurites) proper.<sup>13</sup> Plexiform neurofibromas are seen in a

younger age group, frequently being present at birth. They are most commonly found about the head, face, and neck. Because of their proximity

FIG. 3.

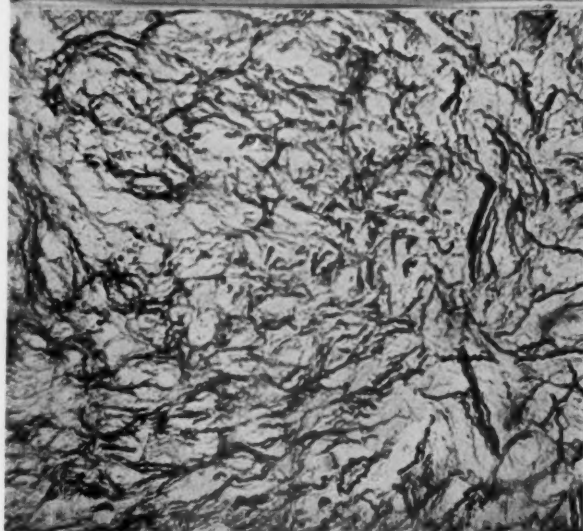
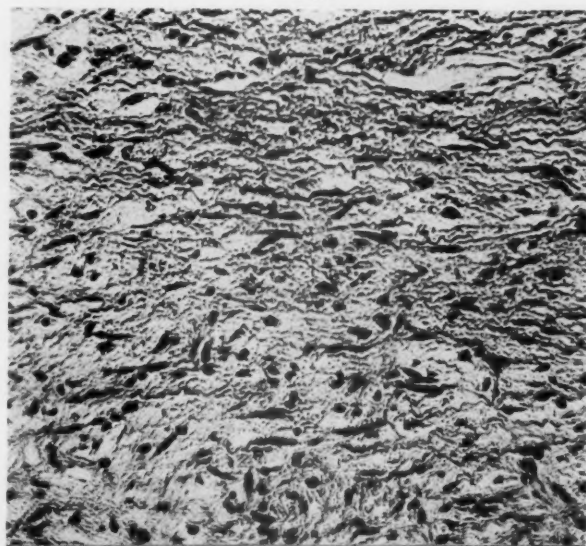


FIG. 4.

FIG. 3.—Case 11, J. S.: Photomicrograph of a retroperitoneal neurolemmoma demonstrating the reticular type of architecture (Antoni Type B tissue). (Masson's trichrome stain)

FIG. 4.—Case 11, J. S.: Photomicrograph, following Perdrau's method of silver impregnation, demonstrating the fine reticular architecture and the larger wavy collagen fibers of the microscopic section shown in Figure 3.

to important structures, and the fact that they extend far along the nerve trunk within the perineurium, complete local excision is often impossible.

*Neurofibromas.*—The term neurofibroma has been used by us to include



those nerve sheath tumors which are usually found associated with a hereditary generalized neurofibromatosis (von Recklinghausen's disease). In this condition, there is a congenital disturbance of the nerve sheaths resulting in multiple subcutaneous nodules, tumors of the deeper nerve trunks, and patchy pigmentated areas. These patients often have associated skeletal disturbances and mental deficiency. The neurofibromas may, upon occasion, be isolated tumors.

Structurally, the neurofibromas differ from neurolemmomas in that there are bands of elongated spindle cells occasionally arranged in whorls but which often have no characteristic arrangement. They differ further in that there is a larger component of fibrous and fibroblastic tissue (Fig. 5). There is little doubt that in the neurofibroma, there is a proliferation of both the cells of the sheath of Schwann, and those of the endoneurium and perineurium, while the neurolemmomas are composed primarily of Schwann cells. Neurofibromas, likewise, may become malignant and give rise to spindle cell sarcomas. The incidence of sarcomatous proliferation in neurofibromas associated with von Recklinghausen's disease has been quoted by Hosoi<sup>14</sup> as being about 13 per cent.

*Ganglionated Neurofibromas.*—Ganglionated neurofibromas (Fig. 6) may be either neurolemmomas or neurofibromas. They are tumors arising from the sheaths about ganglia. The ganglion cells are of an adult type and take no active part in the tumor growth. They differ from ganglioneuromas, in that the latter are relatively differentiated neuroblastic tumors in which the tumor cell is the ganglion cell and commonly have associated with them the more immature cells of the sympathoblast and neuroblast. The abdominal ganglionated neurofibromas are invariably retroperitoneal tumors. They are slowly growing and well encapsulated. Because of their location, they usually have obtained considerable size when first diagnosed and are consequently removed with difficulty.

*Neurogenic Sarcomas.*—As to the origin of neurogenic sarcomas, there are two possibilities. One is that they arise upon neurolemmomas; the other is that they arise as sarcomas. In support of the first view are the numerous cases reported in the literature in which incomplete excisions of neurolemmomas have resulted in malignant lesions later. Also, in cases of neurogenic sarcomas examined for the first time, areas may be found in which the original architecture of the neurolemmoma is preserved (Fig. 7 A and B). In support of the second view are those small incidental tumors removed at time of other operations, which histologically are shown to be sarcomatous. The most convincing evidence favors the first view. The criterion of the neurogenic origin of these sarcomas was based upon the presence in them of areas characteristic of neurolemmomas. There were many other abdominal tumors that undoubtedly were neurogenic in origin but were not included because of the lack of demonstrable evidence.

The neurogenic spindle cell sarcomas do not have the same prognostic significance as other types of malignancies. Our experience closely simulates



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that of others, that even though they are reported as malignant, in the majority of cases they fail to give rise to distant metastases but tend to remain locally malignant. Stout found that 74 per cent (48 of 65 cases) of peripheral nerve

FIG. 5.

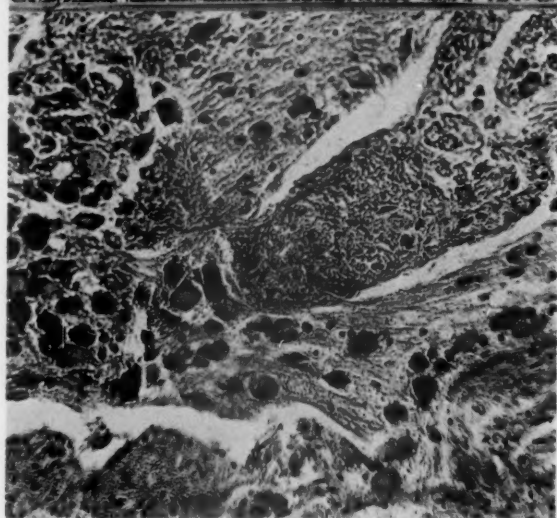
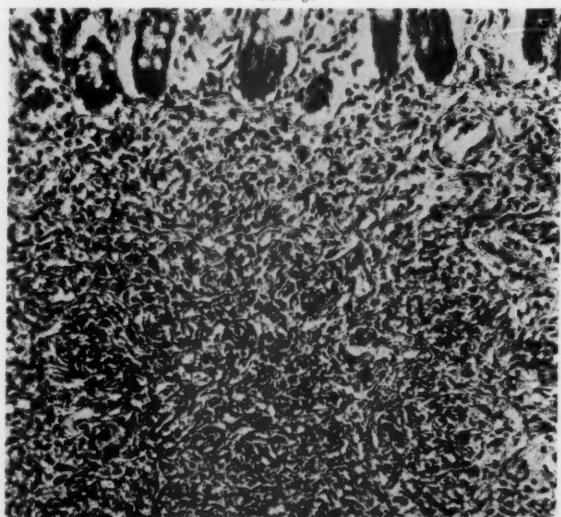


FIG. 6.

FIG. 5.—Case 7, D. G.: Photomicrograph of an intestinal neurofibroma showing the irregular pattern of schwannian and fibroblastic tissue.

FIG. 6.—Case 12, J. S.: Photomicrograph of a ganglionated neurofibroma showing the presence of mature ganglion cells.

neurogenic tumors recurred following excision but in only 20 per cent (18 of 91 other similar cases) did they show evidence of metastases.

*Gross Characteristics of Neurogenic Sarcomas.*—Grossly, these neoplasms are of two types depending upon their location: The first are the large,

diffusely infiltrating neoplasms found in the retroperitoneal regions and mesenteries; and the second, the sarcomas found either in the gastro-intestinal tract, or incidental to other lesions for which the operation was performed.

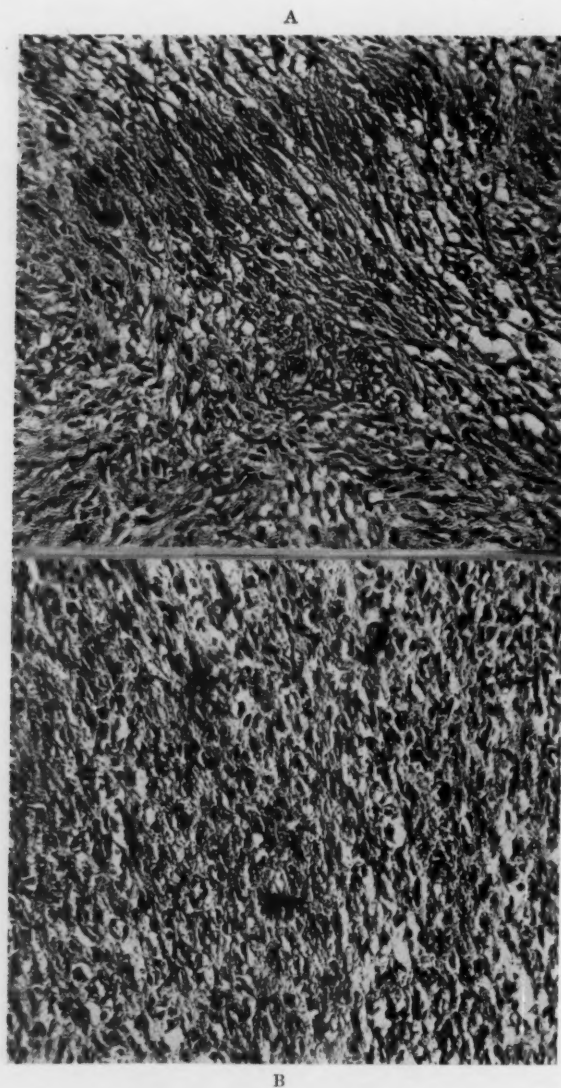


FIG. 7 A.—Case 3, L. P.: Photomicrograph of the benign region of a gastric neurogenic sarcoma (Fig. 11 A) which demonstrates the palisading and reticular type of tissue. (Mallory's phosphotungstic acid hematoxylin stain)

B.—Case 3, L. P.: Photomicrograph of the sarcomatous region of the gastric neurogenic sarcoma (Figs. 11 A and 7 A) demonstrating the loss of the original type of architecture.

The first group is characterized by a large, nodular, solid (occasionally cystic), knotted mass that can be palpated diffusely infiltrating the adjacent organs, and often matting intestinal coils together. The cut surface usually shows

large, soft, necrotic areas appearing yellow, and other red hemorrhagic and cystic areas. The cystic areas contain a gelatinous substance. No evidence of encapsulation is noted. The second type, which are usually found arising in the gastro-intestinal tract, are often hour-glass or oval in shape, solid in consistency, and encapsulated except for an occasional break in the capsule where infiltration is seen. The sarcomatous proliferation may take place within the tumor and no evidence of an infiltrative border be present. This is especially true of the neoplasms arising upon the serosal surface.

*Histopathology of Neurogenic Sarcomas.*—Histologically, the neurogenic sarcomas are composed of rather plump, hyperchromatic spindle cells with an occasional mitotic figure (Fig. 7 B). The cells and nuclei may be of

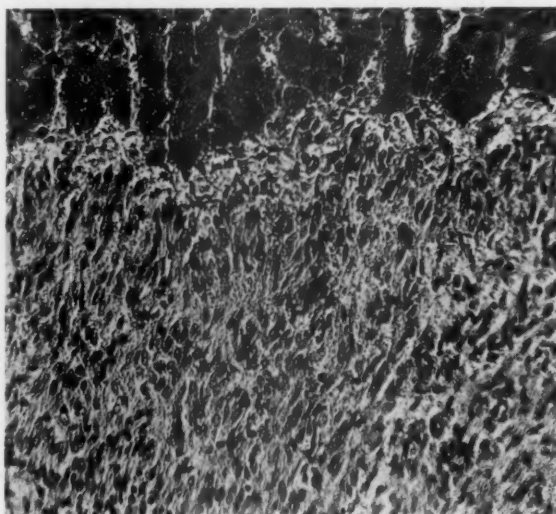


FIG. 8.—Case 9, D. E.: Photomicrograph of an hepatic metastasis of the mesenteric neurogenic sarcoma seen in Figure 15. Section demonstrates suggestive palisading even in the metastases. (H and E stain)

various shapes and are less differentiated than those seen in the neurolemmoma. The cytoplasm is often scanty. The larger portion of the neoplasm has no characteristic architecture which would differentiate it from other spindle cell sarcomas. However, there usually persist certain areas of whorling, interlacing bands of cells or palisades which identify its origin (Fig. 7 A). For the most part, palisade formation is either scant, just suggestive (Fig. 8), or entirely absent. The reticulin as well as the larger wavy collagen fibers are decreased in number and size. It has been reemphasized by Stout that the greater the number and thickness of the collagen fibers, the slower the growth will be, and the less likely the occurrence of metastasis.

*General Clinical Features of Neurolemmomas, Neurofibromas and Neurogenic Sarcomas.*—Since the neoplasms under discussion arise from the investing sheaths of peripheral nerves, both somatic and sympathetic, it is possible,

theoretically at least, for them to occur in all parts of the body. Clinical observations, as evinced by the many cases recorded in the literature, show that the tumors have a predilection for certain sites such as the neck and the extremities, and that they are not uncommon in the thorax. Generally speaking, they are not frequently encountered among the structures of the abdominal cavity. With regard to their incidence in the various portions of the alimentary tract, again curious differences are noted. Thus, while certain organs such as the esophagus, colon and rectum seem to be singularly immune, in the stomach these tumors are relatively common. Unlike many of the more commonplace abdominal neoplasms, the neurogenic tumors are often discovered in unusual or even bizarre places such as the mesenteries, omenta or retroperitoneal spaces. Since they are expansively growing neoplasms, as their size increases, even in the case of the nonmalignant lesions, adjacent structures such as the stomach, intestine or colon may become secondarily involved in the neoplastic process. Such secondary involvement at times necessitates extensive or formidable operative procedures in order to eradicate the growth completely.

Even in the unmistakably malignant lesions (neurogenic sarcoma), distant metastases do not take place until relatively late in the disease. In only three of the eight neurogenic sarcomas in this series were distant metastases observed. Thus, since even the sarcomatous lesions tend to remain localized for a long period of time, prompt recognition of their presence and radical surgical removal will very frequently be followed by good end-results. Since the dividing line between the neurolemmoma and the neurogenic sarcoma is a somewhat arbitrary one, depending largely upon the degree of cellularity of the growth, and infiltrative tendencies, and since different areas of the same tumor may exhibit different histologic features, none of these tumors is to be regarded as entirely innocent, and prompt surgical removal of any such tumor is urgently demanded. It seems more than likely that a neurolemmoma may, at any time during its life history, assume malignant properties and become capable of giving rise to distant metastases. Study of the microscopic sections in several of our cases affords convincing evidence of this fact. This same point has been stressed by Harrington,<sup>15</sup> who reports excellent results from surgical treatment in a comparatively large series of intrathoracic neurofibromas. He believes that early removal is clearly indicated since sarcomatous proliferation may take place at any time.

In our own personal experience the results from surgical treatment of the various forms of internal nerve sheath sarcoma have been more satisfactory than has been the case when dealing with similar lesions situated on the surface of the body and particularly with those arising from the large nerves or nerve trunks of the extremities. From a review of the literature, one gains the impression that others have had similar experience.

*Neurogenic Tumors of the Stomach.*—Of the 18 neurogenic lesions comprising the series, six were neurolemmomas, three neurofibromas, eight neurogenic sarcomas, and one a ganglionated neurofibroma (Table II). Seven

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TABLE II

Neoplasm	No. of Cases
Neurolemmoma.....	6
Neurofibroma.....	3
Neurogenic sarcoma.....	8
Ganglionated neurofibroma.....	1
Total.....	18

of these were located in the stomach, three in the intestines, two in the mesenteries, and six in the retroperitoneal space (Table III).

TABLE III  
DISTRIBUTION

Location	No. of Cases
Stomach.....	7
Intestine.....	3
Mesenteries.....	2
Retroperitoneal space.....	6
Total.....	18

Due to the confusion which exists in terminology, the meager data presented in many of the case reports, and the differences of opinion among pathologists in the interpretation of their histopathology, it is difficult to estimate, with any degree of accuracy, the total number of cases of neurolemmoma and neurogenic sarcoma of the stomach which have been reported. In this connection, it is of interest to refer to certain of the more important communications of the various aspects of tumors of the stomach, which have appeared in the literature during recent years. Eusterman and Senty,<sup>16</sup> in 1922, reported 27 cases of benign tumors of the stomach from the Mayo Clinic. They found the myomas and fibromas to constitute the largest groups, whereas no mention was made of tumors of neural origin. Eliason and Wright,<sup>17</sup> in 1925, in a similar study, reported no instances of neurogenic tumors in their series of 50 cases. In their experience papillomas and polyps were the benign lesions most frequently encountered. In 1926, Balfour and Henderson<sup>18</sup> presented the data in 58 cases of benign gastric neoplasms. While none of the tumors were classified as of nerve sheath origin, nevertheless 23 of the tumors were designated as fibromas, myomas, fibromyomas, adenoyomas and myxofibromas, a closely related group.

Arthur Purdy Stout (1935), in a very comprehensive discussion of the benign nerve sheath tumors, critically appraises the evidence submitted in the gastric tumors of neurogenic origin, previously reported. He accepts 32 cases as being truly nerve sheath tumors and to these adds three cases of his own. In a later communication concerned with the malignant tumors of the peripheral nerves, he included two additional cases, namely, those of Hartman and Shouldice.

Geschickter,<sup>19</sup> in 1935, in his study of tumors of the digestive tract, found



among 962 malignant lesions, ten examples of nerve sheath sarcoma, three of which occurred in the stomach.

Minnes and Geschickter<sup>20</sup> (1936), studying benign tumors of the stomach, mentioned 102 cases of neurofibroma among 931 cases of benign tumors reported in the literature. They concluded that neurofibromas of the stomach were not infrequent and calculated that such tumors constituted approximately 10.9 per cent of the recorded cases of benign gastric lesions. In their own series of 50 benign tumors from the Johns Hopkins Hospital, there was

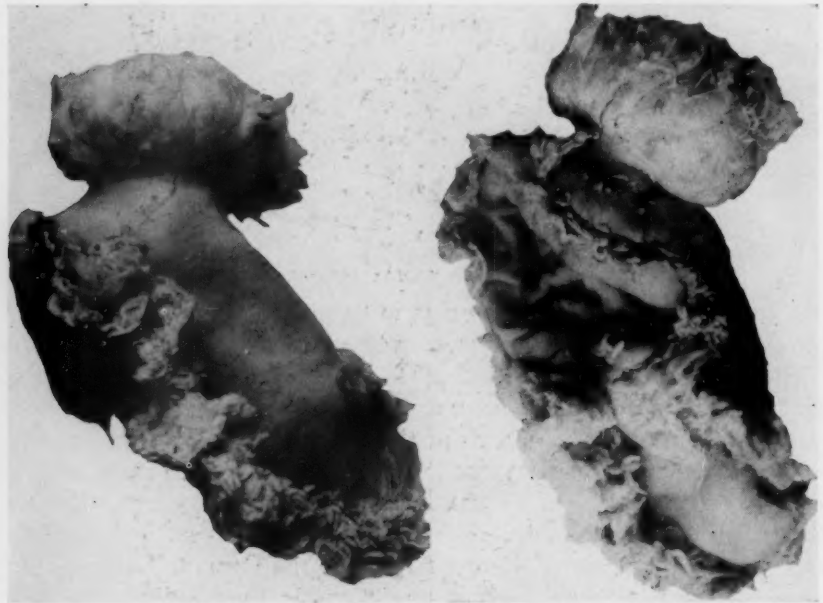


FIG. 9 A.—Case 1, O. B.: Photograph of an hour-glass neurolemmoma located upon the posterior wall near the greater curvature of the stomach.

one large neurofibroma accidentally discovered in a 78-year-old man who died of a ruptured bladder.

In two recent Cabot cases (No. 21112<sup>21</sup> and 23312<sup>22</sup>), the clinical records of patients with neurogenic sarcoma of the stomach are presented. In the former case, the patient, a man, age 46, gave a history of ulcer symptoms of long duration with repeated hemorrhages more recently. A spindle cell neurogenic fibrosarcoma was successfully removed at operation. The second case was that of a 64-year-old woman whose chief trouble was vomiting of blood over a five-year period. A neurogenic fibrosarcoma of the stomach was surgically removed.

In general these nerve sheath tumors are more apt to be encountered along the lesser curvature of the stomach and more often in the antrum or at the pyloric end of the viscus than in the cardia. There are conflicting statements in the literature regarding the frequency of involvement of the

## NEUROGENIC TUMORS OF ABDOMEN

anterior and the posterior gastric walls. On account of the greater ease of inspection and palpation of the anterior wall, it seems probable that more of the small incidental lesions have been recognized when in this location.

In the case of the benign lesions growth is usually slow, although, ultimately, such tumors may attain great size and become readily palpable through the abdominal wall. From its beginning in the gastric wall as growth proceeds, the tumor may enlarge outwardly forming an extragastric, subserous



FIG. 9 B.—Case 1, O. B.: Roentgenographic appearance of the neoplasm shown in Figure 9 A demonstrating the large, polypoid, rounded intragastric mass.

or even pedunculated tumor. In other instances extension into the gastric cavity takes place resulting in an intragastric submucosal tumor. The mucous membrane becomes thinned-out and frequently shows ulceration over the summit of the tumor, an important point in explanation of the symptomatology and the roentgenographic findings of these tumors. An excellent demonstration of this was observed in Case 3. Growth in both directions results in a tumor of hour-glass or dumb-bell configuration (Figs. 9 A and 10A).

Grossly, these neoplasms are gray, yellowish-gray, or pinkish-gray in color, often with a suggestion of translucency. The mass is ovoid or globular in

shape, and the surface is smooth, although there may be a variable degree of nodulation. On section, the tissue is found to be firm in texture and the

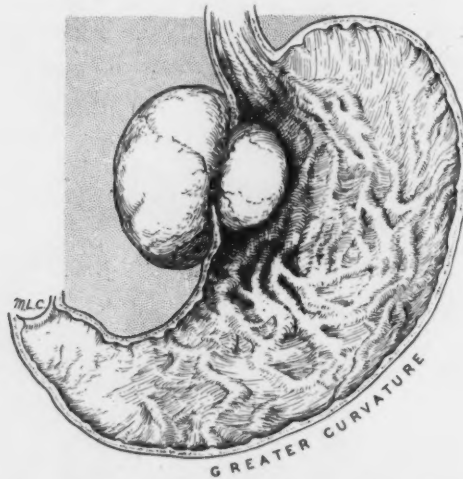


FIG. 10 A.—Case 2, R. B.: Drawing illustrating the large hour-glass neurolemmoma (Fig. 2 A) located upon the lesser curvature near the cardiac end of the stomach.

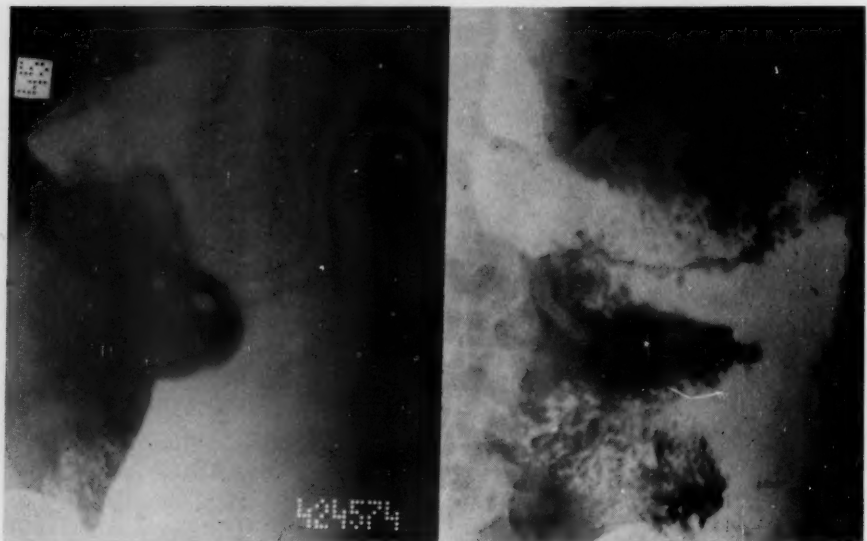


FIG. 10 B.—Case 2, R. B.: Roentgenologic examination, June 8, 1938, demonstrates the appearance of the neoplasm shown in Figure 10 A, with the ulcer crater at the superior aspect. Roentgenologic examination, December 28, 1938, demonstrates the esophagojejunal anastomosis following the total gastrectomy.

growth is well circumscribed at its mural attachment. Occasionally, cystic degeneration may take place, resulting in a large solitary cyst or in some instances in a mass containing multiple smaller cystic cavities.

Not infrequently, smaller lesions are observed, being encountered quite by accident during the course of a celiotomy for some quite unrelated condition, *e.g.*, gastric carcinoma, peptic ulcer, cholelithiasis, *etc.* In our group of seven neurogenic tumors of the stomach, three were of this type, two being removed at the time of partial gastrectomy for carcinoma, and one encountered and removed at the time of celiotomy for gallbladder disease. Of these three incidental tumors, the two associated with carcinoma were neurolemmomas while the third case proved to be a small neurogenic sarcoma.

*Symptoms.*—While there are few if any symptoms which are pathognomonic of these tumors, there are a few complaints, or combinations of complaints, which are common to a fairly large number of the cases. By far the most important and the most suggestive symptom of which these patients complain is hematemesis. This is usually characterized by recurring massive hemorrhages often separated by long intervals of good health. Frequently in addition there are more or less typical ulcer symptoms, occasionally of long duration. Consequently an incorrect diagnosis of bleeding peptic ulcer is often made. The explanation of the bleeding is readily found in the ulceration of the gastric mucosa overlying the tumor (Fig. 11 A). This point has often been stressed in the literature, and the gross finding of ulceration was very striking in several cases in the present series (Cases 2 and 3). Sometimes subjective symptoms may be entirely absent even after a tumor mass is detected. This is particularly apt to be true in the case of lesions with large extragastric extensions. Pyloric obstruction is occasionally noted although its occurrence is dependent largely upon the size and position of the tumor. Rarely a pedunculated intragastric lesion may prolapse through or into the pyloric ring, thereby causing obstructive symptoms. Obviously the small, accidentally discovered tumors produce no symptoms *per se*, or if they do, they are overshadowed by the symptoms relevant to the major disorder.

*Examination.*—Usually, few significant findings are noted on physical examination; in fact, the remarkable feature is the good state of nutrition of the patient in spite of a long history of illness and of repeated hemorrhages. Infrequently an abdominal tumor mass may be felt. Laboratory investigations often reveal a secondary anemia and the presence of occult blood in the stools. The gastric analysis is of relatively little assistance in arriving at a correct diagnosis. By far the most important evidence is to be obtained from roentgenologic study. Especially in the case of lesions on the lesser curvature, the usual findings of benign gastric tumor are seen following the ingestion of the barium meal. Thus, there is apt to be a rounded mass, with a smooth contour projecting into the lumen of the stomach (Figs. 9 B and 10 B). This appearance is exactly the same as that seen in the cases of leiomyoma, and as in the cases of leiomyoma and leiomyosarcoma, the barium often clearly marks the small central ulceration over the tumor responsible for the hemorrhages (Figs. 10 B and 11 B).

*Treatment.*—Wide surgical excision or resection is the treatment of choice.

While local excision may suffice for some of the smaller lesions, in the case of the larger tumors, adequate removal is ordinarily possible only by partial

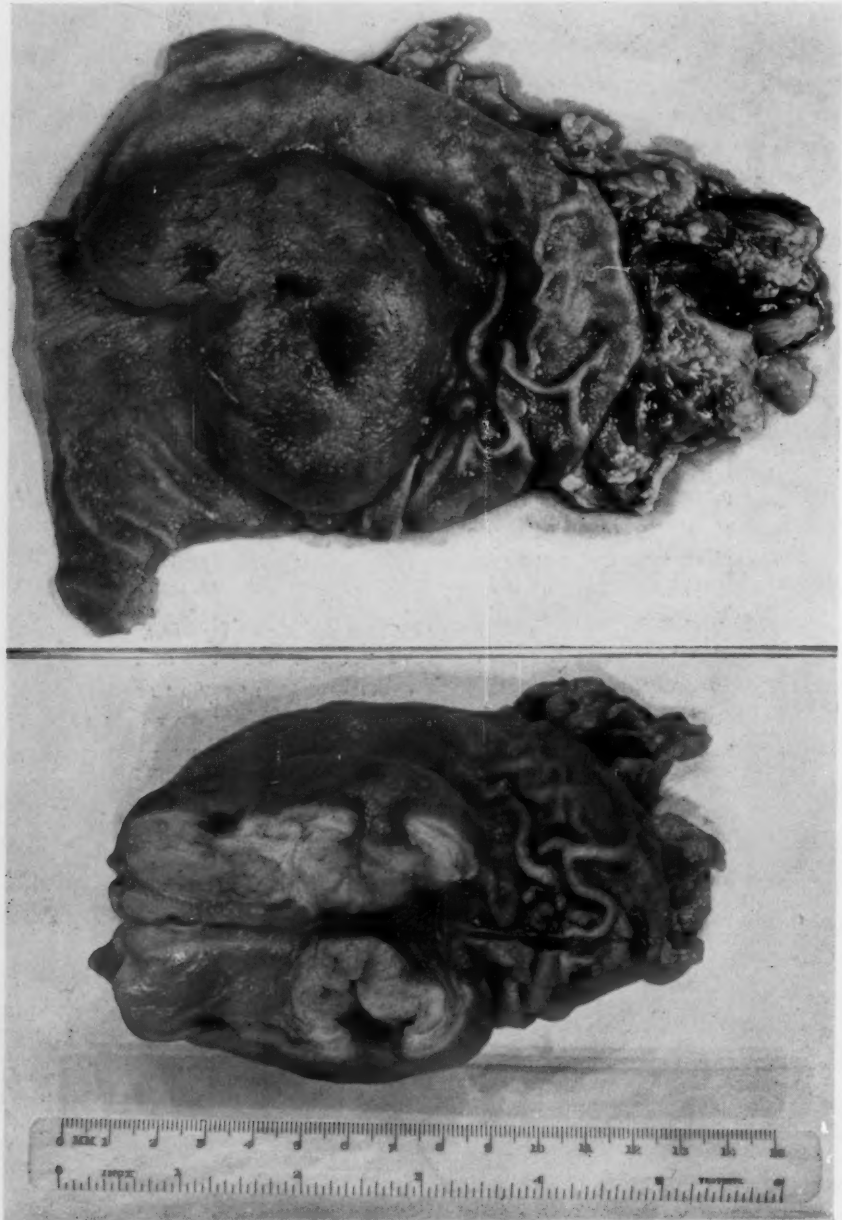


FIG. 11 A.—Case 3, L. P.: Neurogenic sarcoma at the pyloric end of the stomach (Fig. 7 A and B) demonstrating the large ulcer craters and its intramural location.

or even total gastrectomy. While the neurolemmomas tend to recur locally following incomplete operations, if removal is adequate, the prognosis is



usually excellent. Even in the cases of neurogenic sarcoma, the prognosis is reasonably good, providing an adequate resection is performed. Since distant metastasis does not take place at an early date, and since involvement of the regional lymph nodes is not an important matter to be reckoned with, a thorough removal will often effect a cure. In the one case of neurogenic sarcoma, in which the entire specimen was available for study, detailed examination of the cleared specimen for lymph nodes showed no evidence of lymphogenous metastases—in contradistinction to the absence of metastases

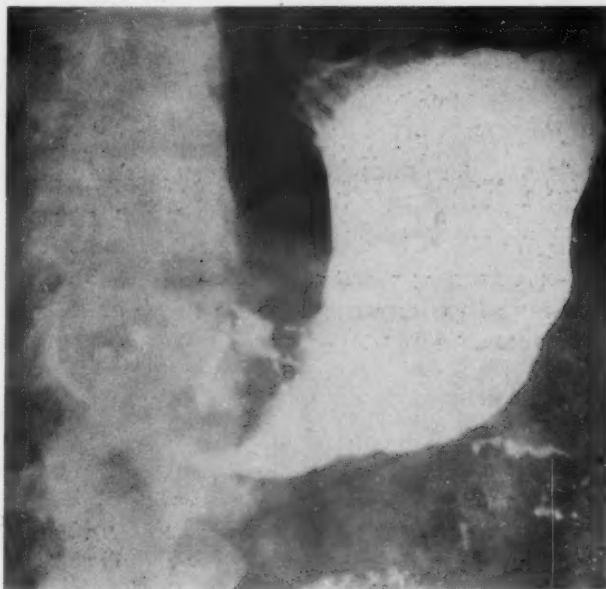


FIG. 11 B.—Case 3, L. P.: Roentgenographic appearance of the neoplasm seen in Figure 11 A demonstrating a large intragastric mass in the pyloric antrum and flecks of barium in the ulcer craters.

in only four of 50 cases of carcinoma of the stomach studied in a similar manner. In fact, the prognosis is distinctly better than in the case of carcinoma of the stomach of the same magnitude.

Seven tumors of nerve sheath origin were situated in the stomach in our series, three of these being of sufficient cellularity to warrant a diagnosis of neurogenic sarcoma. The remaining four tumors were neurolemmomas (Table IV). All were isolated tumors, and none of the patients in this group showed any of the stigmata of von Recklinghausen's disease. In each of the four cases in which the neurogenic tumor was the primary and sole lesion, the chief complaint was that of massive hemorrhages. In two of these cases partial gastrectomy was performed, whereas in one, total gastrectomy was necessary due to the high position of an hour-glass tumor on the lesser curvature. In the remaining case, a very large tumor which arose from the posterior wall of the stomach filled the omental bursa and was firmly adherent to the posterior wall of the bursa over a large area. Removal was impossible,

TABLE IV

## NEUROGENIC TUMORS OF STOMACH

Neurolemmoma.....	4
Primary lesion.....	2
Incidental.....	2
(Gastric Ca.)	
Neurogenic sarcoma.....	3
Primary lesion.....	2
Incidental.....	1

*Symptoms*

Hemorrhage.....	4
None (tumor incidental).....	3

and only a sufficient amount of tissue for biopsy was removed by means of the electrosurgical loop. Microscopic examination showed this to be a neurogenic sarcoma. There were no deaths in this group of gastric neoplasms. The following case abstracts illustrate the important clinical features of primary neurogenic tumors of the stomach:

ABSTRACTS OF CASE REPORTS ILLUSTRATING IMPORTANT CLINICAL FEATURES  
OF PRIMARY NEUROGENIC TUMORS OF THE STOMACH

**Case 1.**—O. B., white, female, age 37, a Russian-Jewish housewife, was admitted to the hospital, April 30, 1936, with a complaint of gastric hemorrhages. She had been quite well until one month prior to admission, when she suddenly felt nauseated and vomited a large quantity of blood. Subsequently she passed several tarry stools. Two days later she experienced a second episode of bleeding. There was no antecedent history of abdominal pain or discomfort, and there had been no digestive symptoms. Since the onset of the trouble she had been on a strict ulcer dietary regimen. Roentgenologic studies elsewhere revealed a lesion in the stomach, thought to be a carcinoma.

There were no significant findings on physical examination. Laboratory studies showed the urine to be normal, the Kahn reaction of the blood to be negative and the leukocyte count to be 4,500, with a normal differential. The erythrocyte count was 2,800,000 and the hemoglobin content 52 per cent. The gastric analysis showed absence of free hydrochloric acid. The reaction of the stool to the benzidine test was negative. Roentgenologic examination disclosed a rounded, lobulated mass within the lumen of the stomach, situated just above the midpoint. It was considered to be a polypoid, primary gastric neoplasm (Fig. 9B).

Because of a slight upper respiratory infection, she was discharged from the hospital, May 6, 1936, and returned for operation, May 11, 1936. A celiotomy was performed, May 14, 1936. The lesion in the stomach was located near the midpoint. It proved to be an hour-glass type of tumor, with a large intragastric projection and a larger extragastric portion of the tumor extending into the omental bursa. It was removed by means of a high gastric resection. Convalescence was uneventful except for a slight wound infection which responded promptly to treatment. She was discharged from the hospital, June 7, 1936. She returned for examination, July 7, 1936, feeling well and in excellent health. She was last heard from, April 23, 1940, at which time her general condition was excellent.

*Pathologic Examination\**—*Gross:* The specimen was a segment of stomach 11 cm.

\* The restudy of the gross and microscopic specimens of all cases reported, and the present interpretation of the latter, after subjecting them to newer staining methods, has been undertaken by Dr. Earle B. Kay.

long. Near one end there was a large mass with a smooth surface. This apparently arose within the wall of the stomach. It appeared as two connected nodules. One measured 6x5x3 cm. and protruded into the lumen. The other was subserous and measured 6x7x3.5 cm.

*Microscopic:* The neoplasm is composed of spindle cells having plump, oval nuclei arranged in interlacing bands and whorls. An occasional area suggestive of palisading, but no true palisades are found. A large portion of the neoplasm is reticular in character. Perdrau's silver stain demonstrates a very fine reticulin. Very few larger collagen fibers noted. Masson's trichrome stain clearly demonstrates the histologic features of the Schwann cell with its pink protoplasmic anastomosing end processes which are encased in a thin sheath of greenish-blue collagen. Mallory's phosphotungstic acid hematoxylin stain shows the Schwann cells with blue-staining nuclei, pink cytoplasm and the cytoplasmic end processes ensheathed in a layer of orange collagen. *Pathologic Diagnosis:* Neurolemmoma.

**Case 2.**—R. B., white, female, age 40, a Jewish housewife, was admitted to the hospital, June 7, 1938, complaining of attacks of vomiting blood. The first episode occurred one year prior to entry, and at this time tarry stools were also noted for several days following the vomiting of a large quantity of blood. A second attack occurred six months previously and a third one three weeks before admission. Since the last attack she had noticed shortness of breath, palpitation, and ease of fatigue. There had been no appreciable weight loss. The physical examination disclosed no significant findings. The urine was normal. Gastric analysis (with histamine) showed the presence of free hydrochloric acid in normal amounts. The reaction of the stool to the benzidine test was positive (four plus). Blood examination: Leukocytes 6,700, with 56 per cent polymorphonuclear leukocytes; erythrocytes 4,430,000; hemoglobin 58 per cent. The total plasma proteins were 4.9 mg. per cent. The albumin was 3.0 mg. per cent and the globulin 1.9 mg. per cent, with an A/G ratio of 1.6. The plasma chlorides were 574 mg. per cent. The Kahn reaction of the blood was negative. Roentgenologic examination showed a gastric neoplasm involving the upper portion of the lesser curvature, and normal visualization of the gallbladder (Fig. 10 B). A peritoneoscopic examination, made June 15, 1938, showed no evidence of metastatic carcinoma in the liver and no peritoneal implantation metastases.

Accordingly, celiotomy was performed, June 20, 1938. High on the lesser curvature of the stomach was an hour-glass-shaped tumor, one portion of which projected into the cavity of the stomach and the other into the peritoneal cavity. The upper portion of the tumor mass was only about 3 cm. from the junction of the stomach with the esophagus. Removal was accomplished by total gastrectomy. Convalescence was uneventful and she was discharged from the hospital, July 14, 1938. At the time of her last visit to the Out-Patient Department, in November, 1939, her condition was found to be satisfactory, and check-up roentgenologic studies showed the esophagojejunal anastomosis to be functioning properly.

*Pathologic Examination.*—*Gross:* (Fig. 10 A) The specimen measured 19 cm. along the greater curvature and 12 cm. along the lesser curvature. On the lesser curvature, and at the uppermost part of the specimen, was a tumor mass measuring 8x7x2.5 cm. This was nodular and firm. It appeared to arise in the wall and raised both the serosal and the mucosal surfaces involving them. The mucosal surface was pitted but not grossly ulcerated. There was no evidence of invasive spread.

*Microscopic:* (Fig. 2 A) Large encapsulated, expansively growing neoplasm showing marked palisading of the nuclei with tendency to whorl formation. The tumor is very vascular. Many of the whorls are arranged about blood spaces. The cells are spindle-shaped with round, plump nuclei. A small amount of pink-staining cytoplasm with anastomosing end branches forming a syncytium is seen. Perdrau's silver stain shows fine reticulin which is separated by large bands of collagen. Masson's trichrome stain demonstrates again the pink-staining spindle cells giving rise to pink-staining syncytial fibrils. Scat-

tered throughout the section are irregularly dispersed green and greenish-blue collagenous fibers. Mallory's phosphotungstic acid hematoxylin stain demonstrates the spindle cells with their plump, blue nuclei and diffuse chromatin granules, and the larger collagen fibers are stained orange brown. *Pathologic Diagnosis:* Neurolemmoma.

**Case 3.**—L. P., white, male, age 51, a merchant, was admitted to the hospital, February 13, 1940, complaining of dizziness, fainting spells and blood in the stools. For one year previously he had noticed progressive weakness. One month before entry, while at work, he suddenly fainted, and following this he passed a large tarry stool. A few days later a similar episode occurred. A roentgenologic examination, made elsewhere, resulted in a diagnosis of a bleeding gastric ulcer, being made, and he was placed on an ulcer dietary regimen with amphogel. One week prior to admission, check-up roentgenograms were taken, during which examination he fainted. He had lost no weight, and gave no history of nausea or vomiting. However, he had experienced slight epigastric pain following meals. This had been relieved by food and soda.

Physical examination disclosed no significant findings. The urine was normal. The leukocyte count was 4,000; the erythrocyte count 2,500,000, with a hemoglobin content of 30 per cent. The guaiac test of the stool was positive. Gastric analysis showed free hydrochloric acid in normal amounts. The Kahn reaction of the blood was negative. Roentgenologic studies showed an irregular filling defect in the distal third of the stomach (Fig. 10 B). The appearance was that of a gastric carcinoma. Following three blood transfusions, a celiotomy was performed, February 20, 1940. A large mass was found in the anterior wall of the stomach in the prepyloric region. This appeared to be a benign tumor. It was removed by partial gastrectomy. The postoperative course was uneventful. He was discharged from the hospital, March 11, 1940.

*Pathologic Examination.*—*Gross:* (Fig. 11 A) The specimen consisted of the lower portion of the stomach. Upon the anterior wall there was a large intramural neoplasm measuring 8x6x3 cm., which extended down to the pylorus. In the center of the neoplasm were three deep ulcers extending through the mucosa down to the neoplasm.

*Microscopic:* (Fig. 7 A and B) A cellular neoplasm showing areas of palisading; other areas show whorls and reticular architecture. Masson's trichrome and Mallory's phosphotungstic acid hematoxylin stains demonstrate the Schwann cells with their anastomosing protoplasmic ramifications. Fine reticular net work seen between the cells. A large portion of the neoplasm has undergone sarcomatous proliferation with loss of the original architecture. Such regions show closely packed hyperchromatic spindle cells in no characteristic arrangement. The mucous membrane overlying the neoplasm shows ulceration, the ulcer craters penetrating deeply into the underlying tissue. *Pathologic Diagnosis:* Cellular neurolemmoma with areas of neurogenic, spindle cell sarcoma.

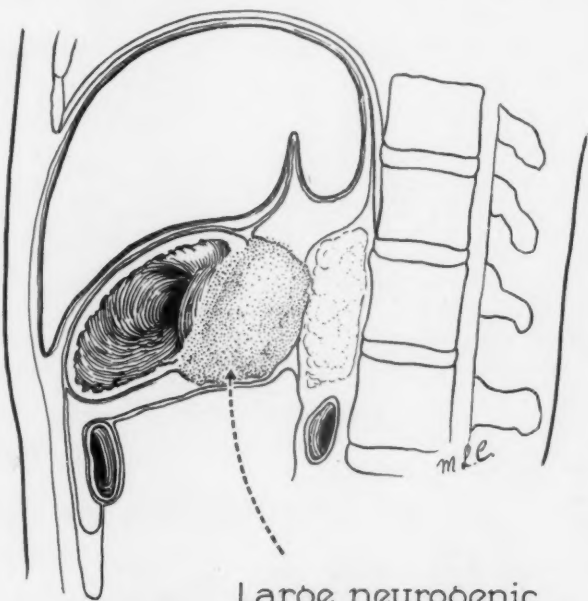
**Case 4.**—J. P., white, male, aged 35, an Austrian bricklayer, was admitted to the hospital, May 10, 1931, complaining of headaches, midepigastric pain, and vomiting of blood. His health had always been excellent until two years previously, when he began to have pain following meals, the pain being relieved by food and soda. Fourteen months previous to his admission he had had a severe gastric hemorrhage. At this time, he had vomited a large amount of blood and had fainted. He was treated elsewhere for three weeks. Roentgenologic studies at that time showed evidence of a peptic ulcer. He was placed upon an ulcer dietary regimen, with alkalis. He adhered to this for nearly a year, during which time his health had remained fairly good. Three weeks before admission he noticed that the stools were tarry and there was a recurrence of the epigastric pain. Three days before his admission, he had another severe hemorrhage. Following this he had been able to eat practically nothing and was so weak that he had to remain in bed nearly all of the time. While he had gradually gained in weight during the past year, there had been a considerable weight loss during the past few weeks.

Physical examination revealed marked pallor of the skin and mucous membranes. In the epigastrium, just below the xiphoid, there was an area approximately 6 cm. in diameter which was markedly tender to palpation. No masses could be felt. The urine was

## NEUROGENIC TUMORS OF ABDOMEN

normal. The leukocyte count was 8,800, with 61 per cent polymorphonuclears; the erythrocyte count was 2,040,000, with a hemoglobin content of 30 per cent. The Kahn reaction of the blood was negative. The reaction of the stool to the benzidine test was positive on four occasions. Gastric analysis revealed the presence of free hydrochloric acid in approximately normal amounts. Roentgenologic examination showed the chest to be normal and there was no evidence of abnormality to the gastro-intestinal tract.

The clinical diagnosis was bleeding peptic ulcer or possibly a bleeding carcinoma of the stomach. After several transfusions his condition improved and a celiotomy was performed, June 24, 1931. The lower half of the stomach was found to be normal while in the upper half, posteriorly, there was a large mass about twice the size of a man's fist. It extended upward to the diaphragm but was not adherent to it. The tumor practically filled the omental bursa and was firmly attached posteriorly, thus fixing the



Large neurogenic sarcoma of posterior wall of stomach invading retroperitoneal tissue.

FIG. 12.—Case 4. J. P.: Drawing illustrating a neurogenic sarcoma upon the posterior wall of the stomach which fills the lesser omental bursa and invades the pancreas.

stomach to the vertebral column (Fig. 12). On account of its position and size, removal seemed to be out of the question and accordingly with the electrosurgical loop, a small portion of the tumor was removed for biopsy.

The postoperative convalescence was prolonged but on the whole was satisfactory. There was one massive hemorrhage from the stomach, on the thirteenth postoperative day. He was discharged from the hospital, July 25, 1931. He was last seen January 13, 1932, when he returned for check-up examination. At that time his condition was essentially unchanged.

*Pathologic Examination.*—*Microscopic:* The tumor is cellular neoplasm composed of spindle cells. Certain areas show palisading. Other areas have a cylindromatous architecture with whorl formation about blood vessels. *Pathologic Diagnosis:* The neo-



plasm is cellular enough to be considered a neurogenic spindle cell sarcoma arising upon a neurolemmoma.

These case records demonstrate some of the problems involved in treatment. The first case was a neurolemmoma, adequately removed by a high subtotal gastrectomy; and the second, a similar lesion but one so situated as to require total gastrectomy. The third case was one of neurogenic sarcoma, dealt with by subtotal gastrectomy, while the last case was one of a far advanced, inoperable neurogenic sarcoma arising from the posterior gastric wall (Table V).

TABLE V  
NEUROGENIC TUMORS OF STOMACH

<i>Treatment</i>	
Partial gastrectomy.....	2
Total gastrectomy.....	1
Exploration biopsy.....	1
Excision incidental.....	1
Removed—Resection for Ca. (incidental).....	2
Total.....	7

*Tumors of the Intestine, Colon and Rectum.*—In the portion of the digestive tract distal to the stomach, neurogenic tumors are extraordinarily rare. The reports of only a very few such lesions of the small intestine, colon and rectum are to be found in the literature. Stout, in his critical survey of the field in 1935, recognized the following cases as acceptable (Table VI):

TABLE VI  
Author Location of Tumor

<i>Benign (neurolemmoma)</i>	
Delagénière	Duodenum
Lemmonier and Peycelon	Duodenum
König	Small intestine
Leriche	Small intestine
Nordlander	Small intestine
Lhermitte and Leroux	Cecum
Peritz	Appendix
<i>Malignant (neurogenic sarcoma)</i>	
Adrian	Duodenum
Kohtz	Duodenum
Hartmann	Small intestine

At this time Stout believed that there was no case of neurogenic tumor of the colon or rectum which could be considered authentic.

T. S. Raiford<sup>23</sup> (1932) found no instances of neurogenic tumor in his study of 88 cases of tumors of the small intestine, from the Johns Hopkins Hospital material. Likewise Rankin and Newell<sup>24</sup> (1933) make no mention of such lesions in their review of 35 cases of benign tumors.

S. A. Goldberg<sup>25</sup> (1939) reported ten cases of unusual intestinal tumors. No neurogenic tumors other than one argentaffine tumor of the jejunum were included. Cohn, Landy, and Richter<sup>26</sup> (1939) reported seven cases of tumors of the small intestine, none of these being neurogenic in origin.

Geschickter<sup>12</sup> (1935), in his study of tumors of the digestive tract, found only ten neurogenic sarcomas among 962 malignant lesions. Three of these occurred in the small intestine and four in the rectum. He states that, microscopically, these tumors resemble the more common neurogenic sarcomas of peripheral nerves. In one of his cases, a tumor of the small intestine was associated with multiple subcutaneous nerve sheath tumors of the von Recklinghausen type. This author, also, in a discussion of his group of 178 benign tumors, refers to a group of ten "lipomas, fibromas, and neuromas." The exact location of these lesions is not mentioned. More recent reports include the Cabot Case No. 24011,<sup>27</sup> and a case reported from the Mount Sinai Hospital by Klingenstein<sup>28</sup> (1938). The former was that of a 62-year-old male, who was found, at operation, to have a neurogenic fibrosarcoma of the ileum. The clinical features of the case had been bleeding and the development of a pelvic tumor. The lesion, which was described as being the size of the operator's fist, was successfully resected. Grossly, it resembled the leiomyomas found in the stomach, inasmuch as there was an area of deep ulceration in the mucosa over the central part of the tumor.

Klingenstein's patient was a 29-year-old female, who had had repeated episodes of severe bleeding from the intestine, the cause of which proved to be an ulcerated neurofibroma of the ileum. The tumor was successfully resected.

Miller and Frank<sup>29</sup> (1939) reported two instances of neurofibrosarcoma of the intestine. The first was a 72-year-old female, whose only symptoms were those related to a pelvic tumor which proved, at operation, to spring from the jejunum. The tumor, a large extralumenar growth, was successfully resected. Microscopic study showed it to be a neurofibrosarcoma. The second patient, a 47-year-old male, complained only of weakness and vague abdominal pains. Celiotomy, and subsequently necropsy, revealed multiple tumors of the entire small intestine. These had produced partial intestinal obstruction in many places. The microscopic examination of all the lesions showed them to be neurofibrosarcomas.

Even more rare are the neurogenic tumors of the colon and rectum. Keith<sup>30</sup> (1937) reported the cases of a 50-year-old female, from whom a tumor, 1x2 cm., of the rectal wall was removed. The sections were examined by Doctor Ewing, who made a diagnosis of neurofibroma.

Woolf<sup>31</sup> (1938) reported the case of a 70-year-old male, who was found to have a tumor lying between the rectum and the coccyx. Operation revealed that this arose in the rectal wall. The tumor was removed and histologic examination showed it to be a neurofibroma.

Glenn<sup>32</sup> (1939) reported a case of neurogenic fibroma of the transverse

colon. The patient was a 25-year-old female, who complained chiefly of frequency of urination and polyuria. An abdominal tumor was present which was localized to the transverse colon roentgenologically. It was successfully resected. Glenn states that, in a careful search of the literature, he was unable to find any other, microscopically verified, neurogenic fibroma of the colon.

In general, the clinical behavior of these tumors in the small intestine is similar to that of most benign tumors. If they are of the intraluminal type, intussusception is apt to occur or obstruction may be produced by virtue of their size alone. The extraluminal growths are usually manifested by the presence of an abdominal or pelvic tumor mass, possibly associated with pressure symptoms. Since there is often ulceration of the intestinal mucosa overlying the tumor, serious hemorrhages may occur, just as in the case of the gastric tumors.

Our series includes three examples of neurofibroma of the small intestine. The following case is one in which a solitary benign neurofibroma of the ileum was responsible for chronic intussusception (Fig. 13 A and B).

**Case 5.**—I. K., white, female, age 60, a Finnish housewife, entered the hospital, October 30, 1939, complaining of abdominal pain and backache. Her symptoms began four months prior to admission. One month after the onset, a cervical polyp was removed elsewhere. Tissue examination showed no malignancy. She was not relieved and her symptoms had increased in severity, the pain localizing in the right lower quadrant. In addition, frequency of urination, urgency and nocturia had developed. Bimanual examination revealed in the anterior portion of the pelvis, and chiefly on the right side in the region of the bladder and extending out laterally, a cylindric, firm tumor mass which was very freely movable. Motion of this did not seem to impart any motion to the fixed uterus or cervix. Rectal examination was negative. The urine was normal. The Kahn test of the blood was negative. The leukocyte count was 7,500, and the hemoglobin content 70 per cent.

Roentgenologic studies showed: (1) Normal colon; (2) normal upper gastro-intestinal tract; (3) faint visualization of the gallbladder, with at least one large nonopaque calculus. Thorough visualization of the urinary tract, including cystoscopy and retrograde pyelograms, yielded negative findings. A clinical diagnosis of a cyst or malignant neoplasm of the right ovary was made. A celiotomy was performed, November 18, 1939. At this time, a mass was noted in the midileum which proved to be an intussusception. This was reduced and a tumor about the size of an English walnut could then be palpated within the lumen of the bowel. A segment of ileum, approximately 25 cm. in length, was resected and an end-to-end anastomosis performed. The postoperative course was stormy. On the tenth day a fecal fistula developed. On December 13, 1939, an attempt was made to close the fistula. This was unsuccessful. She developed general peritonitis and died, December 14, 1939. A necropsy was not obtained.

*Pathologic Examination—Gross:* (Figs. 13 A and B) The specimen consisted of a segment of small intestine measuring 25 cm. in length, with attached mesentery. Eight centimeters from one end, on a pedicle 1 cm. long, there was an ovoid, firm, smooth mass, measuring 6.5x3.5x3 cm. The cut surface was pale, pinkish-gray, shiny, homogeneous, and moderately firm. There was considerable whorling. Some slight evidence of hemorrhage was noted at the distal end of the tumor and also at two points in the wall of the bowel.

*Microscopic:* A loose textured, edematous neoplasm composed of Schwann cells and fibrous tissue in no characteristic arrangement. Much of the architecture is reticular in character. Many large, wavy, collagen fibers are seen throughout the neoplasm. *Pathologic Diagnosis:* Neurofibroma.

FIG. 13 A.

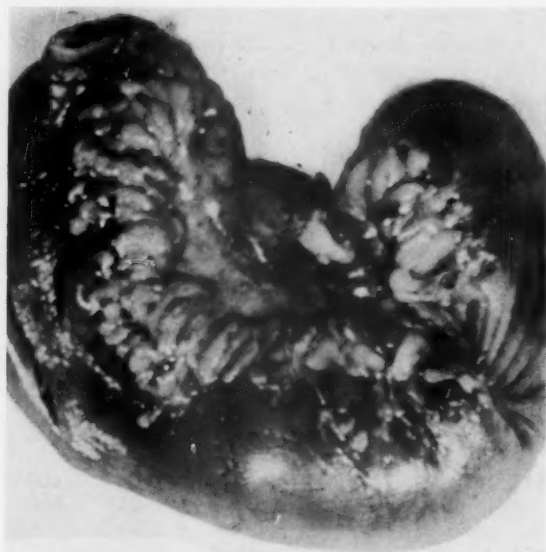


FIG. 13 B.

FIG. 13 A.—Case 5, I. K.: Photograph of the segment of resected small intestine showing the intussusception.  
B.—Case 5, I. K.: Photograph of the large pedunculated neurofibroma which caused intussusception noted in Figure 13 A.

The intestinal lesion in this case proved to be a large pedunculated neurofibroma. No history of bleeding was obtained.

The other two examples of neurofibroma of the small intestine in the series were discovered at necropsy and the intestinal lesion in these cases was but one of the local manifestations of a general neurofibromatosis. In one case, two small neurofibromas of the jejunum were found in a young man who had extensive plexiform neurofibromatous involvement of the prostate, periprostic tissues, buttocks and left thigh. This case has been reported in detail elsewhere (McDonnell<sup>33</sup>). The other patient, a 15-month-old female, who died shortly after being admitted to the hospital, was found to have a congenital disturbance of the sympathetic nervous system with both angioneurofibromas and neurofibromas of the sympathetic nerves, involving the anterior and posterior mediastinum, celiac plexus, and the nerves of the small and large intestine (Fig. 5). This was believed to be a form of von Recklinghausen's disease. No lesions on the surface of the body were noted. The abstracts of these two cases follow:

**Case 6.**—G. H., white, male, age 30, a truck driver, was first seen in November, 1928, at which time he presented multiple subcutaneous nodules over the entire body. They were most marked on the posterior aspect of the thighs, the scrotum and the prepuce. The skin overlying these tumescences presented a diffuse, brown, macular eruption. There was an atrophic, undescended testis in the left inguinal canal. A diagnosis of von Recklinghausen's disease was made, and at this time the tumor mass on the posterior aspect of the left thigh was excised. Convalescence was uneventful. Microscopic examination of the tissue removed showed the lesion to be a congenital cirroid neurofibroma, or "fibroma molluscum." He returned in January, 1931, complaining of rectal pain due to pressure of the tumor masses in the left buttock. At this time, neurofibromas were removed from the left buttock and an anal plastic operation was performed. A circumcision was also performed in order to correct the phimosis due to the neurofibromatosis of the penis, the redundant foreskin being twice the length of the shaft. He again returned in July, 1935, because of acute urinary retention. He had been catheterized intermittently by his physician. He was semistuporous. The physical examination was essentially the same as on the previous admission except for the presence at this time of costovertebral tenderness. The bladder was considerably distended. The Kahn reaction of the blood was negative. The leukocyte count was 12,700; and the hemoglobin content 95 per cent. The urine contained albumin (three plus). There were many red and white blood cells as well as bacilli. The blood nonprotein nitrogen was 200 mg. per cent, and the plasma chlorides were 331 mg. per cent.

During his hospital stay, the bladder was gradually decompressed and continuous indwelling catheter, drainage was maintained. His general condition was so poor that diagnostic cystoscopy was not deemed advisable as a means of determining the cause of the vesical outlet obstruction. It was believed, however, that a vesical submucous neurofibroma similar to the cutaneous lesions might be responsible for the obstructive phenomena. His condition gradually grew worse, and he died, August 12, 1935.

**Necropsy.**—The important findings were: (1) Neurofibromatosis (von Recklinghausen's disease). (2) Extensive cirroid neurofibromatous infiltration in and about the prostate, prostatic urethra, bladder, seminal vesicles, and penis. (3) Neurofibromas of the vagus and intercostal nerves and jejunum. There were two neurofibromatous nodules in the wall of the jejunum, each about 1 cm. in diameter. (4) Cirroid neurofibroma of the left buttock and thigh with scars of partial excision. (5) Right nephrolithiasis. (6) Ascending chronic purulent and ulcerative cystitis, ureteritis; and



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pylelonephritis. (7) Advanced pyonephrotic atrophy of both kidneys. (8) Bilateral hematogenous, fibrinopurulent lobular pneumonia.

*Pathologic Examination.—Microscopic:* The neoplasm in the jejunum is composed of Schwann cells with their anastomosing protoplasmic ramifications. Abundant fibrous stroma. Dispersed throughout the tumor are irregularly-shaped hyalin bodies simulating those seen in meningiomas. *Pathologic Diagnosis:* Neurofibroma. *Prostate:* Throughout the prostate and periprostatic tissues is a diffusely infiltrating plexiform neurofibroma.

**Case 7.**—D. G., white, female, age 15 months, was brought to the hospital, July 19, 1930, because of weakness, emaciation, and marked pallor. The mother stated that this condition had been present since shortly after birth. She was a "blue baby" and one of twins. Examination revealed cardiac enlargement, and an enlarged liver. Temperature 103° F. The Kahn reaction of the blood was negative. The leukocyte count was 13,000, with 55 per cent polymorphonuclear leukocytes; the erythrocyte count 1,700,000; and the hemoglobin content 18 per cent. A blood transfusion was administered at once. Her condition grew rapidly worse and she died that evening.

*Necropsy.*—(1) Congenital disturbance of the sympathetic nervous system probably related to von Recklinghausen's disease. Multiple knotted, twisted, grape-like masses along course of the vagus nerves and celiac plexus. Knotted mass in posterior mediastinum, 4.5x3.5x1 cm. in diameter. Throughout the small and large intestines are multiple, small conglomerate, purplish nodules, some of which hang free in the intramesenteric fat. Some are firmly attached to the intestinal wall and appear to lie between the muscularis and the mucosa. (2) Extreme congestion of lungs and brain. (3) Fibroid atrophy of thymus. (4) Fatty liver. (5) Patent ductus arteriosus and foramen ovale. (6) Horseshoe kidney with double ureter.

*Pathologic Examination.—Microscopic:* (Fig. 5) The multiple tumor masses are composed of angiomatous and angioneurofibromatous masses of young nerve sheath tissue. Typical Schwann cells can be seen as demonstrated by Masson's trichrome and Mallory's phosphotungstic acid hematoxylin stains. An abundant amount of reticulin and fibrous tissue is noted within the neoplasms. *Pathologic Diagnosis:* Multiple neurofibromas of small and large intestines.

In one of the three cases of neurogenic sarcoma exhibiting metastases, a large primary lesion was found in the pelvis (Case 18). The diagnosis of neurogenic sarcoma was made from tissue obtained from a rectal biopsy. Since death occurred a few weeks later from exsanguination due to massive hemorrhages from the rectum, it is entirely possible that this tumor arose from the rectal wall; yet positive proof is lacking and in view of the rarity of such tumors in the rectum, the case has been placed in the retroperitoneal group.

*Tumors of the Mesenteries.*—As previously mentioned, tumors of the type under discussion are frequently found in unusual or out-of-the-way places. Examples of such odd situations are the mesenteries and omenta. Since Rankin and Major<sup>34</sup> were able, in 1932, to report 22 cases of tumors of the mesenteries and cite several hundred similar cases in the literature, it is evident that mesenteric tumors are not excessively rare. Warren and Sommer,<sup>35</sup> in a study of sarcoma of the soft parts, found 63 neurogenic sarcomas, four of which were in the abdominal region. One of these was situated in the mesentery. Further details of the case are not given. Moreover, instances of tumors of the greater omentum are reported from time to time. Nevertheless, the fact that in our small series of 18 nerve sheath tumors

(four of which were merely incidental findings) there should be two tumors in such locations would seem to be of some significance. One of these cases was a huge neurolemmoma arising in the gastrocolic omentum, and the second was a neurogenic sarcoma developing in the mesentery of the terminal ileum. The abstracts of these cases are appended:

**Case 8.**—G. K., white, male, age 43, a Canadian salesman, entered the hospital, July 22, 1937, with the complaint of pain in the left upper quadrant and a tumor mass in the abdomen. One month previously, because of vague abdominal discomfort, he consulted a physician, who discovered the mass in the upper abdomen. There had been no change in bowel habit, no abnormalities of the stools, and no weight loss. Examination disclosed a globular, slightly tender and slightly movable mass about the size of a grapefruit situated in the epigastrium. The urine was normal. The Kahn test of the blood was negative. The leukocyte count was 8,500, with 70 per cent polymorphonuclear leukocytes; the erythrocyte count, 5,470,000, and the hemoglobin content 107 per cent. The blood bilirubin was 4 mg. per 1,000 cc. and the fasting blood sugar was 72 mg. per cent. Roentgenologic studies revealed: (1) A normal chest; (2) normal gallbladder visualization without stone; (3) normal colon; (4) no intrinsic gastric or duodenal lesion but evidence of pressure from a large extra-alimentary tumor possibly arising in the pancreas (Fig. 14B). The preoperative clinical diagnosis was pancreatic or omental cyst.

A celiotomy was performed, July 26, 1937. The tumor was found to be solid in character and to have arisen in the gastrocolic omentum. It involved a portion of the greater curvature of the stomach and also the transverse colon (Fig. 14A). Complete removal was accomplished by resecting the lower half of the stomach by the Pólya method and by an obstructive resection of the involved segment of the transverse colon. Convalescence was uneventful and he was discharged from the hospital, August 14, 1937. He returned to the hospital, October 6, 1937, and a closure of the temporary colostomy, resulting from the obstructive resection of the colon, was performed. Again the convalescence was uneventful, and he was discharged, October 26, 1937. He was last seen, June 2, 1938. He was free from symptoms, and entirely well except for a slight ventral hernia in the surgical scar.

*Pathologic Examination.*—*Gross:* The specimen consisted of a portion of omentum, measuring 27x22 cm., in which there was a firm, round, encapsulated mass measuring 14x8x6 cm. This mass was attached to the wall of a segment of stomach 9 cm. in length. The mucosal surface was smooth and not infiltrated. On the opposite side of the tumor was attached a segment of colon 7 cm. in length.

*Microscopic:* A large neoplasm showing whorling and interlacing cords of cells. Areas of palisading noted. Much of the tumor is reticular in structure (Fig. 2B). Masson's stain demonstrates the special histologic characteristics of a nerve sheath tumor. *Pathologic Diagnosis:* Neurolemmoma.

**Case 9.**—D. E., white, male, age 52, a mail carrier, was first seen, November 8, 1937, complaining of pain in the abdomen. Three years previously he had had an appendectomy for right lower quadrant pain. Following this he was well for a year, whereupon he again developed sharp pains in this same region. In June, 1937, a mass was discovered in the lower abdomen. Shortly after this he experienced an attack of intestinal obstruction, which was relieved by nonoperative measures. There had been no melena or hematemesis. The tumor mass had gradually increased in size and there had been a slight weight loss.

Physical examination revealed a firm, nontender, movable mass, measuring approximately 6x6 cm., in the right lower quadrant. Rectal examination was negative. The urine was normal. The leukocytes numbered 11,000, with 68 per cent polymorphonuclear leukocytes, and the erythrocytes 4,200,000; the hemoglobin content was 68 per cent. A barium enema showed no intrinsic lesion of the colon. The preoperative, clinical diagnosis was probable abdominal lymphoblastoma.

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Operation was performed, November 19, 1937. In the mesentery of the terminal ileum near the cecum was a large rounded mass, slightly nodular on its surface, lying between the peritoneal leaves. It measured approximately 15x8 cm. There were also

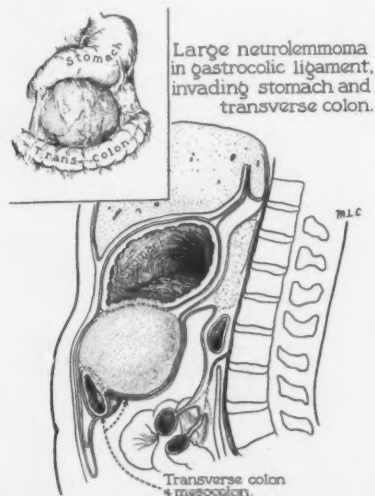


FIG. 14 A.—Case 8, G. K.: Drawing illustrating a large neurolemmoma of gastrocolic ligament (Fig. 2 B) invading the stomach and transverse colon.



FIG. 14 B.—Case 8, G. K.: Roentgenographic appearance of the neoplasm illustrated in Figure 14 A demonstrating the arch formed by the stomach, duodenum and transverse colon about the tumor mass.

several enlarged lymph nodes in the mesentery. The tumor was quite movable and could be delivered into the wound. At both ends of the mass the small intestine was firmly adherent to it. The tumor was excised and short segments of intestine at the two ends resected with end-to-end anastomoses. The postoperative convalescence was stormy; and the clinical picture was that of general peritonitis. He died, December 6, 1937.

Necropsy revealed complete gangrene of the small bowel and its mesentery. Metastases of the neoplasm were found in the liver and on the subdiaphragmatic peritoneum.

*Pathologic Examination.—Gross:* The specimen consisted of a large nodular tumor mass, which measured 15x8x7 cm. Two segments of small intestine, measuring 10 cm. in length at one end and 9 cm. in length at the other, were intimately attached to the tumor mass. The mass appeared to arise within the mesentery but had involved the intestinal wall at one point (Fig. 15).

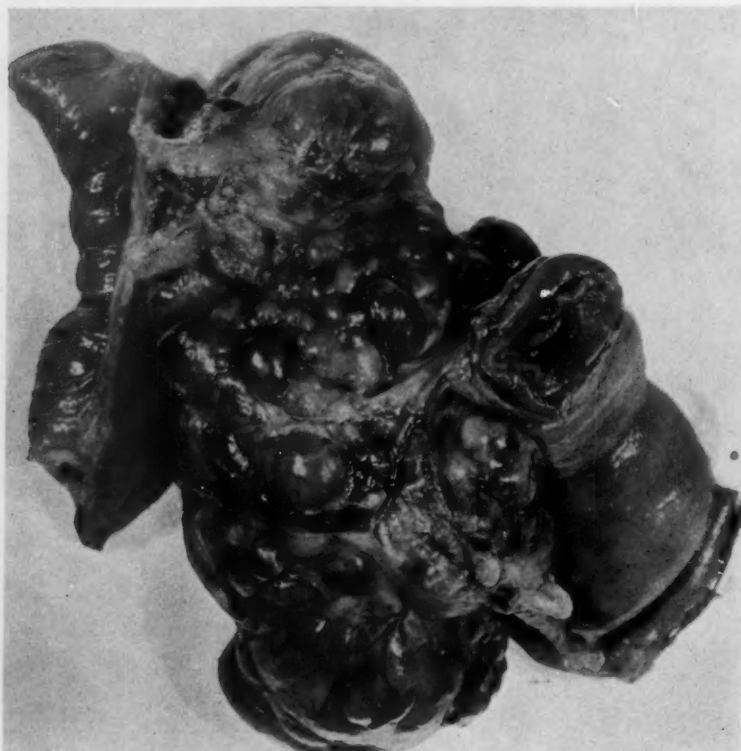


FIG. 15.—Case 9, D. E.: Photograph of a large, nodular, mesenteric neurogenic sarcoma which had invaded two segments of small intestine. Hepatic metastases were demonstrated at necropsy (Fig. 8).

*Microscopic:* A cellular neoplasm composed of elongated spindle cells, arranged in both interlacing cords and whorls. Other parts of the tumor are composed of reticular areas. Mallory's phosphotungstic and hematoxylin stain demonstrates the spindle cells, with large oval, plump blue-staining nuclei with a scant amount of pinkish-brown-staining cytoplasm which extends at both ends into cytoplasmic ramifications which appear to anastomose with similar fibrillae from adjacent cells. These fibrillae appear to be ensheathed in orange, collagenous material. *Pathologic Diagnosis:* Neurogenic sarcoma arising in a neurolemmoma. Metastasis in liver. *Microscopic:* It will be noted that by comparing the hepatic metastasis with the primary neoplasm that the metastatic lesion is definitely more cellular. The cells are shorter and more plump. The reticulin is seen with difficulty. There are areas that are suggestive palisading (Fig. 8). *Pathologic Diagnosis:* Metastatic neurogenic sarcoma.

The first case is practically identical with the one reported by Schrager<sup>36</sup>

(1939). His patient was a 40-year-old female, who also presented herself for examination on account of a large abdominal tumor. It was removed by an operative procedure similar to that described above. The case affords a good example of the involvement of adjacent viscera by a neurolemmoma (Fig. 14 A). While an operative procedure of considerable magnitude was necessary in order to insure complete removal of the tumor, an excellent result was obtained. In view of the benign character of the lesion as indicated by the histologic studies, further trouble on this score seems unlikely. Clinically, our case was also of interest in showing how such a neoplasm may be present for a long period of time, and reach a large size, and still provoke relatively few symptoms.

The second case illustrates some of the technical difficulties attendant upon removal of large tumors of the mesentery (Fig. 15). This case was one of three in the series in which distant metastases from a neurogenic sarcoma were found.

*Tumors of the Retroperitoneal Tissues.*—Retroperitoneal tumors are not especially rare and many types of tumors found in this location have been described. This great variety of lesions can be readily understood by considering the various retroperitoneal tissues which may give rise to new growths. These include connective tissues, blood vessels, lymphatics, lymph nodes, fat, and the various structures of the sympathetic nervous system. While many of the tumors such as the lymphoblastomas, the teratomas and the neuroblastic tumors of the sympathetic nervous system are quite hopeless, there is a considerable number of retroperitoneal tumors which are benign or tend to be of local malignancy only, and hence amenable to surgical attack. To this latter group belong the majority of the nerve sheath tumors. That the neurogenic tumors constitute but a small percentage of the total number of retroperitoneal new growths is evinced by the fact that they are not mentioned in the communications on this subject by Trout and Meekins,<sup>37</sup> or Hansmann and Budd.<sup>38</sup> Judd and Larson<sup>39</sup> (1933) reported 48 retroperitoneal tumors from the Mayo Clinic. Only one of these was of neurogenic origin—it being a paraganglioma which had developed in the suprarenal gland, a type of tumor beyond the scope of the present paper. Unusual cases of nerve sheath tumors in this region, cited by Stout, are those of Virchow, Eichhoff, Pescatori, Erb, Frank, Krekeler and Krumbein, Moreau and van Bogaert, and Pana.

Warren and Sommer<sup>35</sup> found two of their four abdominal neurogenic sarcomas to be situated in the retroperitoneal space, while one was described as being in the pelvic region, and probably should also be included here.

Frank<sup>40</sup> (1938), in a splendid review of the subject, has summarized the literature and has tabulated the important data concerning 107 tumors found in the literature from 1925 to 1932. He carefully excludes tumors arising from abdominal organs (liver, pancreas, adrenals, intestines, genital or urinary organs) as well as mesenteric and omental growths. Also, neoplasms arising from residual urogenital embryonic rests are not considered. Frank's com-



piled group contains 20 neurogenic retroperitoneal tumors, or 18.7 per cent of the total. On the basis of histologic classification, these 20 tumors fall into the following groups: (a) Neurinoma—seven; (b) neurogenic sarcoma—three; (c) ganglioneuroma—six; (d) sympathoblastoma—four. It is only with the first two types that the present discussion is concerned. The operative mortality in this collected group of 20 tumors was 22 per cent, in contrast with no deaths in the group of 28 benign fibromas, lipomas, cysts, *etc.*, and a 28.13 per cent mortality for the general group of sarcomas (38 cases).

In the present series of cases, there were six neurogenic tumors of the retroperitoneal space. Of these, there were four neurogenic sarcomas, one neurolemmoma, and one ganglionated neurofibroma. Surgical removal was possible in four instances, the extirpation, apparently, being complete in two cases, whereas in the other two it was necessary to leave a portion of the base of the tumor due to its proximity to important structures such as the great vessels, bladder or rectum. In the remaining two cases, only a small amount of tissue for biopsy purposes was removed. In one instance (Case 18) this was secured by means of proctoscopy, from a lesion involving the rectal wall, and in one (Case 17), tissue was obtained at the time of an exploratory celiotomy for what proved to be an inoperable retroperitoneal neurogenic sarcoma with extensive metastases to the mesenteric lymph nodes.

The two following cases are of special interest because of the remarkable roentgenologic and operative findings in one, and the unusual clinical history in the other.

**Case 10.**—E. J., white, male, age 47, a laborer, was first seen, June 15, 1933, complaining of constipation, nervousness, nausea and vomiting. For one year he had noticed increasing constipation. For the past six months he had been troubled with abdominal distention, much flatus, and increasing weakness. Following meals there had been a dull pain in the right upper and the left lower quadrants of the abdomen with occasional vomiting spells. He had lost a considerable amount of weight.

Physical examination showed marked pallor of the skin and mucous membranes. A mass was felt which seemed to arise from the pelvis and extend upward almost to the umbilicus and laterally to the outer borders of the rectus muscles. This mass was tympanitic to percussion. There was moderate tenderness over this area. The liver was enlarged. The mass could barely be felt on rectal examination. Sigmoidoscopic examination was negative. Laboratory studies showed the urine and stool to be normal. The leukocyte count was 5,700, with 79 per cent polymorphonuclear leukocytes; the erythrocyte count 3,000,000 with a hemoglobin content of 35 per cent. The red cells showed achromia. The Kahn test of the blood was negative. Roentgenologic examination revealed: (1) No organic lesion of the upper alimentary tract; (2) fistulous communication between small bowel and encapsulated right-sided pelvic abscess; (3) no intrinsic lesion of the colon; (4) foreign body, probably lead shot, within pelvic mass (Fig. 16 B). A clinical diagnosis was made of a pelvic abscess communicating with the small intestine probably due to neoplasm or diverticulitis.

Operation was performed, September 13, 1933. At this time a large tumor was found which was thought to be a sarcoma arising from the pelvis. The upper portion was fairly mobile. At the apex of the mass a loop of small intestine was firmly adherent, and this proved to be the point of communication between the abscess cavity and the bowel, as had been indicated roentgenologically. The tip of the appendix was also adherent to the tumor. At the base of the tumor in the pelvis, posterior to the bladder, the attach-

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ments were extremely firm, and accurate isolation of structures was impossible (Fig. 16 A). In order to mobilize the tumor, the involved coil of intestine was resected and the appendix also removed with the mass. Deep in the pelvis the tumor was so firmly

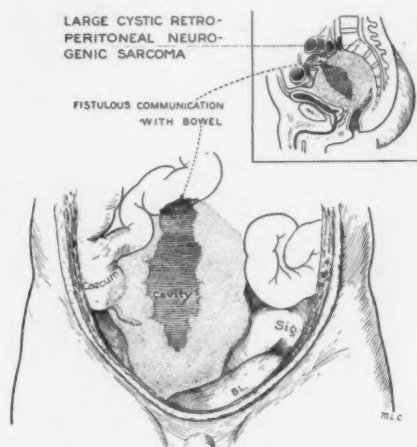


FIG. 16 A.—Case 10, E. J.: Drawing illustrating a large cystic retroperitoneal neurogenic sarcoma having a fistulous communication with the small intestine.



FIG. 16 B.—Case 10, E. J.: Roentgenologic examination, following a barium enema, June 10, 1933, reveals the displacement and compression of sigmoid colon, indicating a large extra-alimentary tumor mass upon the right side of the pelvis and abdomen, as shown in drawing, Figure 16 A. Roentgenologic examination, September 6, 1933, demonstrates a fistulous communication between the small intestine and barium filled cystic space, which was interpreted as an abscess. A small opaque object is noted upon the floor of the cystic space.

fixed that complete excision was impossible. Accordingly, the greater part of the tumor was removed, leaving a small portion of the base behind the bladder. Convalescence was slow but satisfactory. He was discharged from the hospital, November 9, 1933. He was subsequently given a course of deep roentgenotherapy to the pelvis. Following this he

remained in fair health, gradually gaining in weight; and was last seen, April 19, 1935, at which time there was no demonstrable evidence of recurrence or metastasis. Later in the year both legs became paralyzed and he died, September 22, 1935.

*Pathologic Examination.*—*Gross:* The specimen consisted of a hollow tumor mass, the wall of which had been ruptured. The central cavity was lined by an ulcerating, fungating mass of neoplasm which was covered with a thick, foul exudate. The appendix was attached and also a segment of small intestine, the lumen of which communicated directly with the cavity in the tumor.

*Microscopic:* A cellular neoplasm composed of spindle cells showing areas of less complete differentiation in which the cells are polyhedral in form. Other, more differentiated, areas show persistence of original architecture in which there are palisading and whorl formation about the blood vessels resembling a neurolemmoma. Perdrau's silver stain demonstrated a fine reticular structure throughout, Masson's trichrome technic, and Mallory's phosphotungstic acid hematoxylin stains substantiate the nerve sheath origin of this neoplasm. There is infiltration of the intestinal wall with ulceration of intestinal wall and neoplasm on side exposed to intestinal content. *Pathologic Diagnosis:* Neurogenic spindle cell sarcoma.

**Case 11.**—J. S., white, age 49, a fireman, was first seen, February 8, 1938, because of pain in the right leg. This was first noticed about seven years previously. The pain had been most severe on the anterolateral aspect of the thigh. It varied in intensity from a very sharp and severe type to a dull ache, lasting from several minutes to an hour. The attacks of pain occurred every two or three months at first but more recently had increased in frequency. He had noticed little if any weakness in the right leg. In 1927, a diagnosis of syphilis had been made and, at that time, he received an intensive course of antiluetic therapy. The positive physical findings were as follows: (1) Atrophy of the anterior thigh muscles on the right with definite weakness of the iliopsoas. (2) Mild weakness in the right adductors and quadriceps. (3) Right cremasteric reflex diminished. (4) Right knee jerk very weak, left normal. (5) Mild hypesthesia on the right side from L1 to L4 and on the left in L1 and L2. The blood Kahn test was doubtfully positive. The uranalysis was normal and the blood count normal. The cerebrospinal fluid was normal. Roentgenograms of the spine showed a moderate degree of hypertrophic arthritis of the lower dorsal and upper lumbar spine, while the right knee and the chest were normal. Studies of the gastro-intestinal tract and of the urinary tract revealed no abnormalities. Intraspinal lipiodol injection revealed a temporary hesitation of lipiodol at the level of the twelfth and eleventh dorsal vertebrae at which point the lipiodol dispersed into droplets. The findings were interpreted as evidence of a moderate degree of arachnoiditis at the lower dorsal region and the presence of a cord tumor was considered very unlikely. During his stay in the hospital his symptoms improved under bismuth antiluetic therapy. A plaster of paris body encasement was applied to provide complete rest, and he was discharged, March 12, 1938.

He returned, June 8, 1938, at which time his symptoms were as severe as ever. Exploratory laminectomy was advised and performed, June 12, 1938. At this time, no abnormalities of the spinal cord or nerve roots could be ascertained. The posterior divisions of the twelfth dorsal and first and second lumbar spinal nerves were sectioned on the right side. His convalescence was uneventful, and there was slight improvement of his symptoms. In view of the incomplete relief a cordotomy was performed, June 24, 1938. The result of this was fairly satisfactory.

He was next seen, in February, 1939, at which time he complained of a mass in the right lower quadrant of the abdomen. He had lost considerable weight. The mass was easily palpable and seemed quite firmly fixed. Roentgenologic studies of the colon at that time revealed that this was not an intrinsic lesion of the colon, and that the colon was displaced medially. A diagnosis of a retroperitoneal tumor was made and he was operated upon, February 7, 1939. At the time of the celiotomy no significant findings were noted other than a retroperitoneal mass in the right lower quadrant. The posterior

peritoneum was incised and the tumor removed without difficulty. Convalescence was uneventful and he was discharged, February 21, 1939. He was last seen, September 27, 1939, when he was entirely free from pain, showed great improvement in his general health, and examination revealed no signs of recurrence.

*Pathologic Examination.—Microscopic:* (Fig. 3) A well circumscribed edematous tumor composed of Schwann cells, in an arrangement characteristic of Antoni's Type B reticular tissue. Masson's trichrome stain beautifully demonstrates the pink Schwann cells with their protoplasmic ramifications in a syncytial network, each fibril being ensheathed in a thin capsule of bluish-green-staining collagen. Perdrau's silver stain demonstrates the argyrophilic reticulin with large, wavy bands of collagen irregularly dispersed throughout. *Pathologic Diagnosis:* Neurolemmoma.

The tumor in the first case evidently arose in the retroperitoneal or subperitoneal space, becoming wedged in between the bladder and rectum as it increased in size. Neoplastic infiltration of the wall of a loop of small intestine which had become adherent to the mass took place with subsequent perforation and the development of a fistulous communication between the intestinal lumen and the central cystic cavity of the tumor. Removal of the tumor required a resection of the involved segment of small intestine as well as removal of the appendix which was likewise incorporated in the mass (Fig. 16 A).

In view of the incomplete removal of the tumor, postoperative roentgen treatments were given, even though their value was problematic.

The second patient had a long and complicated history and presented a most difficult diagnostic problem. It was not until the abdominal tumor finally became palpable that a correct diagnosis of retroperitoneal tumor was made. The ease of the surgical removal, the benign character of the neoplasm and the marked clinical improvement following removal are matters worthy of note.

The ganglionated neurofibromas should be distinguished from the more common ganglioneuromas, which properly belong to the neuroblastic tumors of the sympathetic nervous system. Our series contained one example of a ganglionated neurofibroma. It was a retroperitoneal tumor situated in the lumbar region just to the left of the midline and occurred in a four-year-old girl. The ganglionated neurofibromas are in fact benign nerve sheath neoplasms which develop in the neighborhood of sympathetic ganglia. As growth of the tumor takes place, ganglia cells become included. Their rôle is entirely passive. The cells are the mature forms and they do not lend malignant characteristics to the lesion (Fig. 6). Similar tumors in the thorax have been mentioned by Andrus,<sup>41</sup> who points out the fact that these tumors are composed of fibrous tissue in the midst of which ganglion cells can be demonstrated. He suggests that it is only by virtue of their situation or point of origin that the ganglion cells are found. The clinical course, treatment and prognosis are essentially the same as in the case of a neurofibroma or neurolemmoma in the same position.

**Case 12.**—J. S., female, aged six, was brought to the hospital by her parents, March 21, 1930, because of a mass in the abdomen. This had been discovered six months



previously during a routine physical examination, and had produced no symptoms. Examination showed the superficial veins of the abdominal wall to be prominent. There was a mass in the left lower quadrant which measured approximately 12x7.5 cm. It was smooth, firm and fixed. It was not lobulated and not tender. Examination of the urine and stool was negative. The leukocyte count was 11,300, the erythrocyte count 4,210,000, and the hemoglobin content 85 per cent. The Kahn reaction of the blood was negative. Roentgenologic studies of the chest, upper gastro-intestinal tract and colon were negative. A diagnosis of retroperitoneal sarcoma was made.

A celiotomy was performed, April 9, 1930. A tumor measuring roughly 7.5x7.5x7.5 cm. was found closely attached to the lateral aspect of the second, third and fourth lumbar vertebrae. The large vessels were close to it. It was found impossible to remove all of the tumor. Consequently, the pedicle was left *in situ*. It would have been impossible to remove this without ligating the vena cava. Convalescence was uneventful. Postoperative deep roentgenotherapy was instituted, and she was discharged from the hospital, May 10, 1930. She was last seen in April, 1940, at which time she was in good health and was developing normally. There was no evidence of recurrence.

*Pathologic Examination—Microscopic:* (Fig. 6) A large encapsulated neoplasm composed of adult sympathetic ganglion cells in an irregularly arranged schwannian and fibrous stroma which appears reticular and edematous in areas, as demonstrated by Masson's trichrome blue and Mallory's phosphotungstic acid stains. *Pathologic Diagnosis:* Ganglionated neurofibroma.

#### ADDITIONAL CASE ABSTRACTS

##### *Neurogenic Tumors of the Stomach*

**Case 13.**—J. D., white, female, age 55, a housewife, entered the hospital, February 16, 1940, complaining of pain in the side and a draining abdominal sinus. Five years previously, following a typical attack of gallstone colic, a cholecystostomy had been performed elsewhere. Many stones were removed from the gallbladder. Four years later, an abscess developed in the scar. This was drained, and since that time there had been persistent drainage of small amounts of clear serous fluid but sufficient in quantity to require constant dressing.

Physical examination revealed a well-healed surgical incision, 12 cm. long, in the right upper quadrant. At the upper angle there was the opening of a small sinus, covered with a crust. There was a large ventral incisional hernia. Laboratory studies showed the urine to be normal, the Kahn reaction of the blood to be positive three plus, and the reaction of the stool to the benzidine test to be positive four plus. The leukocyte count was 7,500, the erythrocyte count 4,850,000, and the hemoglobin content 76 per cent. Roentgenologic studies demonstrated no evidence of an intrinsic lesion of the gastro-intestinal tract other than slight gastric retention at the end of five hours. There was nonvisualization of the gallbladder and no evidence of gallstones.

A diagnosis of recurrent cholelithiasis with occlusion of the cystic duct was made and celiotomy performed, February 20, 1940. A fairly large gallbladder was found which contained white bile but no stones. An exploratory choledochostomy revealed no stones in the common duct. The gallbladder was removed. On the anterior surface of the stomach a small pedunculated tumor was noted. This was about the size of a walnut. It was thought to be a benign tumor and was removed. Convalescence was uneventful and she was discharged from the hospital, March 14, 1940.

*Pathologic Diagnosis.—Gross:* (1) The gallbladder was 9 cm. and practically intact. There were numerous adhesions with considerable thickening of the wall. No stones were present. (2) The specimen from the stomach consisted of a smoothly lobulated, solid piece of tissue measuring 3x2.5x1.5 cm.

*Microscopic:* (1) Old chronic purulent cholecystitis. Marked fibrosis of the gallbladder wall. (2) Hematoxylin-eosin stain demonstrates a cellular neoplasm showing



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short, plump spindle cells with round and oval nuclei. Architecture is that of interlacing bands and whorls of spindle cells. Perdrau's silver stain shows a fine reticulin throughout the tumor. *Pathologic Diagnosis:* Neurogenic sarcoma.

**Case 14.**—F. M., white, male, age 61, a lawyer, entered the hospital, June 30, 1939, complaining of pain in the upper abdomen associated with nausea and vomiting. The symptoms began only five weeks previously. There had been no hematemesis or melena. Since the onset of his trouble his appetite had been poor, and there was a sense of fullness in the stomach following the ingestion of food. There had been a weight loss of 15 pounds (6.8 Kg.). Examination disclosed an ill-defined mass in the midepigastrium which was slightly movable. Urinalysis showed the presence of 20-30 white blood cells per low power field, and a stained smear of the sediment showed many cocci. The Kahn reaction of the blood was negative. The leukocyte count was 8,700, and the erythrocyte count 4,400,000. The hemoglobin content was 78 per cent. Roentgenologic examination revealed an extensive annular neoplasm involving the lower third of the stomach, and normal visualization of the gallbladder by the Graham-Cole test.

A celiotomy was performed, July 3, 1939. A carcinoma was found involving the lower third of the stomach. There was no gross evidence of spread. The adjacent lymphnodes were moderately involved but not extensively so. A partial gastrectomy was performed according to the Hofmeister technic. The postoperative convalescence was uneventful and he was discharged from the hospital, July 21, 1939.

*Pathologic Examination—Gross:* The specimen of the stomach measured 13 cm. in length. Three centimeters from the distal amputation side, on the greater curvature in the prepyloric portion, was 4x3.5 cm. raised, nodular mass with slight ulceration of the surface. It infiltrated through the serosa. At some distance from this lesion, and on the serosal surface, was a smooth, ovoid mass, measuring 2x1x1 cm., which was whitish in color and very firm in consistency.

*Microscopic:* (1) Adenocarcinoma mucosum, Grade II; primary in gastric mucosa. Ulcerating surface. The carcinoma infiltrates entirely through the wall. Numerous signet-ring cells. (2) A neoplasm composed of an edematous architecture of Schwann cells with areas arranged in interlacing bands and whorls characteristic of a neurolemmoma. Slight increase in amount of connective tissue stroma. *Pathologic Diagnosis:* Neurolemmoma.

**Case 15.**—E. H., white, female, age 66, a housewife, entered the hospital, August 2, 1935, complaining of weakness and loss of weight. Her symptoms were of six months' duration. The physical examination was essentially negative except for a questionable mass in the epigastrium. Laboratory examinations showed the urine to be normal. The leukocyte count was 12,800, with 72 per cent polymorphonuclears; the erythrocyte count 4,820,000, and the hemoglobin content 65 per cent. The Kahn test on the blood was negative. Roentgenologic studies showed a partially obstructing lesion involving the distal third to half of the stomach, which was believed to represent carcinoma.

Operation was performed, August 6, 1935. A carcinoma involving the antral portion of the stomach was found. The growth extended 3.5 cm. upward from the pylorus. It involved nearly the entire circumference of the stomach at this point. There were no definitely enlarged lymph nodes along either the greater or the lesser curvatures. Both lobes of the liver, the spleen and gallbladder were normal. The lower half of the stomach was resected by the Pólya method. Postoperative convalescence was uneventful. She was discharged from the hospital, August 24, 1935. She died at home in March, 1937.

*Pathologic Examination—Gross:* The stomach measured 12x9x4 cm. At one end of the specimen the mucosa presented an ulcer 5x3.5x3 cm. The edges were rolled and everted. At the opposite end of the specimen on the serosal surface was a small tumor 2.5x2x1.5 cm. on a narrow pedicle.

*Microscopic:* (1) A well advanced adenocarcinoma infiltrating through the stomach wall into the subserosa. (2) A neoplasm composed primarily of Antoni's Type B reticular tissue. Histologically, small spindle cells with an occasional polyhedral form

are noted, both of which have anastomosing cytoplasmic end processes and are surrounded by a fibrillar network. *Pathologic Diagnosis:* Neurolemmoma.

#### *Retroperitoneal Neurogenic Tumors*

**Case 16.**—R. B., white, male, age 28, a Jewish lawyer, was first seen, March 21, 1928, complaining of a mass in the abdomen. This had been discovered about four years previously. It had caused no symptoms, and there had been no appreciable increase in size. Examination revealed a mass approximately 7.5x6 cm. in the lower abdomen lying near the midline. It extended from 3 cm. above the symphysis to the umbilicus. It was quite firm to palpation and was slightly movable. Laboratory examinations showed the urine to be normal, the leukocyte count 11,600, and the hemoglobin content of the blood 95 per cent. The Wassermann reaction of the blood was negative. The clinical diagnosis was retroperitoneal sarcoma.

Celiotomy was performed, March 28, 1928. Exploration revealed an egg-shaped tumor 15x7.5 cm. lying in front of the promontory of the sacrum between the iliac vessels and in the root of the mesentery of the small intestine. The posterior peritoneum was incised and the tumor easily, and apparently completely, removed. Following operation the convalescence was uneventful except for a slight wound infection. He was discharged from the hospital, April 12, 1928. Subsequently, a course of deep roentgenotherapy was administered. When last heard from, October 22, 1932, his health was excellent and his recovery had been complete.

*Pathologic Examination.—Microscopic:* A neoplasm characterized by interlacing cords and whorls of Schwann cells. Certain areas show evidence of palisade formation. Throughout the neoplasm are seen large wavy collagen fibers. Portions of the neoplasm are becoming cellular enough to be considered sarcomatous. Not likely to metastasize. *Pathologic Diagnosis:* Neurogenic sarcoma.

**Case 17.**—R. H., white, male, age 37, an American farmer, entered the hospital, February 17, 1939, with a chief complaint of indigestion and pain in the abdomen and back. The symptoms had begun two years previously with vague generalized abdominal pain coming on following meals. For about a year he obtained considerable relief on an ulcer dietary regimen, after which time pain and indigestion recurred. Since then, except for periods of temporary relief, he had grown steadily worse. He had lost about 50 pounds (22.7 Kg.) in weight, and had become so weak that he had to give up his work. There had been no nausea, vomiting, or melena. Physical examination revealed a slightly tender, hard, nodular, fixed mass, 7.5x5 cm., in the midepigastrium. The laboratory studies showed a normal urine, and a negative Kahn reaction of the blood. The leukocyte count was 6,000, with 64 per cent polymorphonuclear leukocytes; the erythrocyte count 5,300,000, and the hemoglobin content 86 per cent. Examination of the stool revealed a positive two plus reaction to the benzidine test. Gastric analysis and a glucose tolerance test showed normal values. Roentgenograms showed a normal upper gastro-intestinal tract, normal visualization of the gallbladder, without evidence of included stone, and a normal chest. The barium sulphate enema demonstrated a redundant colon but no evidence of an intrinsic lesion. The clinical diagnosis was retroperitoneal tumor.

Celiotomy was performed, March 3, 1939. The spleen, liver and gallbladder were normal. The stomach, duodenum and kidneys were also normal. The retroperitoneal space, in the midline, was occupied by an extensive, hard, fixed, nodular mass. In the root of the mesentery of the small intestine a number of enlarged, hard lymph nodes were felt. Resection was impossible and no palliative procedure seemed to be indicated. Two bits of tissue were removed for biopsy. The postoperative course was uneventful, and he was discharged, March 20, 1939. He died at home, December 6, 1939.

*Pathologic Examination.—Microscopic:* A very cellular neoplasm composed of coiled columns of Schwann cells giving a palisaded appearance. The histologic characteristics of this neoplasm are best illustrated by Mallory's phosphotungstic acid hema-

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toxylin stain which demonstrates small, flat spindle cells with scant, pinkish-brown-staining cytoplasm extending into a few protoplasmic end processes. The cells appear to be surrounded by a darker staining, yellowish-brown, fibrillar network. Between the coils there is still darker staining, orange-brown collagen. Of two lymph nodes examined, one shows evidence of metastases of the above described neoplasm. *Pathologic Diagnosis:* Neurogenic sarcoma arising in a neurolemmoma.

**Case 18.**—N. L., white, female, age 50, a housewife, was first seen, December 17, 1925, at which time she complained of severe headaches and difficulty in swallowing. Examination showed deafness in the right ear and a moderate degree of bilateral nystagmus. The blood pressure was 148/102. Rectal examination revealed a large nodular tumor mass in the anterior rectal wall 2 cm. from the anal margin. Its upper limit was well above the reach of the examining finger. Adjacent tissues were infiltrated. Proctoscopic examination showed a nodular mass not involving the mucosa. A biopsy was taken from this rectal mass. The urine contained a trace of albumin and many leukocytes per low power field. A neurologic consultant believed the findings to be due to metastases at the base of the skull. No form of surgical therapy seemed indicated and, accordingly, she was discharged, December 23, 1925. Her physician reported that she died at home shortly after her return. Death occurred from exsanguination following several massive hemorrhages from the rectum.

*Pathologic Examination.*—*Microscopic:* A neoplasm composed of whorls and interlacing cords of spindle cells. Parts of the neoplasm are reticular in character, giving the appearance of Antoni's Type B tissue. *Pathologic Diagnosis:* Neurogenic spindle cell sarcoma.

*Summary of Treatment and End-Results.*—Table VII summarizes the treatment carried out in the 18 cases. As will be noted, radical surgical

TABLE VII

## SUMMARY

Location	Type	No. of Cases	Treatment	
Stomach	Neurolemmoma	4	Partial gastric resection	1
			Total gastrectomy	1
			2 cases incidental to carcinoma of the stomach	2
	Neurogenic sarcoma	3	Partial gastric resection	1
			Simple excision	1
			Biopsy	1
Intestine	Neurofibroma	3	Resection segment of small intestine	1
			None (autopsy findings)	2
Mesenteries	Neurolemmoma	1	Partial gastric resection, obstructive resection of transverse colon	1
	Neurogenic sarcoma	1	Resection of 2 segments of small intestine and mesentery	1
Retroperitoneal	Neurolemmoma	1	Excision (complete)	1
	Ganglionated neurofibroma	1	Excision (? complete)	1
	Neurogenic sarcoma	4	Excision (partial)	1
			Excision (complete)	1
			Biopsy	2
Total		18		18

removal was undertaken in ten instances, with two hospital deaths. One of these occurred following resection of a segment of small intestine for a neurofibroma which had caused chronic intussusception, while the other followed the removal of a neurogenic sarcoma situated in the mesentery of the ileum. Of the patients operated upon for gastric lesions, one is entirely well, four years following subtotal gastrectomy for a neurolemmoma; and one, two years following total gastrectomy for a similar neoplasm. The one patient upon whom subtotal gastrectomy was performed for a neurogenic sarcoma was operated upon too recently for the follow-up history to be of significance.

The male patient found to have the large neurolemmoma of the gastocolic ligament which required partial gastrectomy as well as resection of a portion of the transverse colon for its complete removal, was well one year later. Since that time it has been impossible to trace this case.

Complete or partial removal was carried out in four of the retroperitoneal tumors. The one case of neurolemmoma in which complete removal was possible has been followed for only eight months. During this time no evidence of recurrence has been noted. Another patient, having had what was thought to be a complete removal of a neurogenic sarcoma, has been followed for four years and seven months and is entirely well and free from recurrence. The patient who proved to have a retroperitoneal cystic neurogenic sarcoma which involved the small intestine secondarily, died two years following operation, presumably of recurrence. In this case it was realized at the time of the celiotomy that removal had not been complete.

The six-year-old girl who presented the retroperitoneal ganglionated neurofibroma, which was incompletely removed, has remained well for ten years.

#### CONCLUSIONS

Since the nerve sheath tumors which are encountered within the abdominal cavity are chiefly of local malignancy, the prognosis following surgical removal is relatively good. Due to the odd or unusual situations in which they are apt to be found, operations of considerable magnitude are often necessary in order to insure complete removal. The end-results would seem to justify such operative procedures, wherever they are feasible.

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DISCUSSION.—DR. FREDERICK A. COLLIER (Ann Arbor, Mich.): It is obvious that the two types of tumors that have been presented to us in the last two papers are surgical rarities. However, I think they are not so uncommon but that any of us may encounter them at any time. There is very little for me to add, but I should like to emphasize the close clinical relationship between these tumors. They may present a clinical entity and, if such be the case, I think that both types of tumors might well be included in it. It is very difficult, often impossible, for the surgeon who is operating upon one of these tumors to tell whether it is a leiomyoma or whether it is a neurogenic tumor, and I doubt whether anyone can draw the distinction between the two at the time of operation. It is likewise rather difficult for the pathologist to make this distinction.

When Doctor Lahey asked me to discuss his paper, I looked up our cases of leiomyomas and I found three. We then subjected these three cases to stain designed to bring out the changes found in the neurologic tumors. We found that only two of them actually were leiomyomas, while one was a neurogenic tumor, which has been presented in Doctor Ransom's paper.

I wish to present one case of a tumor of the stomach of the neurolemmoma type that can be contrasted with the cases of leiomyoma presented by Doctor Lahey to show that these two pathologic entities present similar clinical and gross pathologic pictures. The roentgenogram and photograph of it are shown under Case 3 in Doctor Ransom's paper. The patient, an obese male, age 51, gave a vague history of indigestion over the past two years. Six months before he came to the hospital, he had a violent hemorrhage, vomiting blood in large amounts. This happened again one month before we saw him. When he arrived in the hospital, his hemoglobin was 28 per cent, but his nutrition was excellent.

The roentgenologic examination was a little puzzling, although the presence of a rather large tumor in the stomach was clear. The gastric acids were within normal ranges. The roentgenographic appearance was highly suggestive of carcinoma but the other factors were somewhat against this diagnosis. He was operated upon and the tumor removed, which, as can be seen, presents a picture that is indistinguishable from some shown by Doctor

Lahey. It proved to be a neurolemmoma. The ulcerations in the mucosa are apparently rather typical of both the leiomyomas and the neurolemmomas. When the tumor was palpated before its removal, it was so freely movable that it gave the sensation of being entirely intragastric. There were excavations in the tumor just beneath the opening in the gastric mucosa, but it was impossible to decide whether the bleeding had come from vessels in the tumor or in the gastric wall.

I believe we must regard these two tumor types as giving similar clinical pictures. If a patient gives a history of severe hemorrhage, has normal gastric acidity, and has a tumor demonstrable roentgenographically, one should think of the possibility of one of these tumors being present. They both have benign and malignant phases and operation should be advised for them. I would like to ask Doctor Lahey whether the tumors in his series were examined by special stains designed to bring out neurofibers. It would be interesting to do this if it has not been done, since some of them might well be neurolemmomas.

DR. JOHN J. MORTON (Rochester, N. Y.): These tumors of neurogenic origin are quite interesting. We have had several of them, I do not know quite how many, and I did not have an opportunity to look them up before I came away. Sometimes when they are in the retroperitoneal position they are very difficult tumors to remove. They are organ-displacing, often very large, and they mold themselves against the spine so that you have no opportunity to develop an edge. They are relatively inelastic and hard to roll over. We operated upon a woman who illustrated how large they may become. Roentgenographically, the mass indented the greater curvature of the stomach, pushed the kidney against the diaphragm, pushed the descending colon toward the midline and flattened out the splenic flexure. It had been slowly increasing in size during the previous six years.

Operation disclosed enormous vessels going into the tumor, and her condition became so bad that we were obliged to stop. Her blood pressure went to where it could not be recorded and we abandoned the operation. After a ten-day delay, I went in again and removed it. The tumor originated in one of the nerve sheaths and was benign. She is well now, seven years since operation.

Only last week, I had another tumor involving the terminal ileum, very similar to one of Doctor Ransom's, which proved to be a neurogenic sarcoma. This tumor occurred in a man, age 55, who gave a history of incomplete intestinal obstruction for over a year. He had complete studies by G.I. series, without finding any evidence of the tumor. But there was persistent blood in the stools and, finally, a movable tumor was demonstrated. Sometimes it could be felt in the abdomen, at other times it would disappear, and then, later on, could be felt in the pelvis. This involved the terminal ileum and it had definite nerve sheaths running to the tumor. There were some evidences of metastases in the nodes leading away from it. Microscopically, it was a fibrosarcoma, which brings me to another point, namely, that these fibrosarcomas are usually locally invasive. They tend to recur locally and to remain local for a long time. I think that we should try to get them out whenever we can because we have an opportunity to really cure these patients.

I recall another patient who was operated upon elsewhere three years before I saw him, with a diagnosis of neurogenic sarcoma involving the lower end of the left ureter. When he was sent to me, this tumor had recurred and it was so enormous it practically involved the whole pelvis. I told the doctor that if it were a neurogenic sarcoma, which I verified from the other hospital,

I did not think it would be radiosensitive and that it was inoperable as far as I could see. He said, "Doctor, you cannot let him down like that. You have got to do something." So I said, "Well, we will irradiate him but it won't do any good." To my surprise the tumor went down from a very large-sized tumor to one about the size of a grapefruit. At that point, he could stand no more radiation. His blood count was in the neighborhood of 2,000 white cells and we could not get it to come up.

It was then decided that we might perhaps be able to get it out. So we catheterized the ureter, and I went in and after fighting through a lot of adhesions, finally got down to the tumor, which was quite well encapsulated. I removed it in pieces. It was a neurogenic sarcoma. Six months later, the man complained of pain around his spine, which was, I thought, of a sort of girdle type, but it occurred to me that it was not correct for this type of tumor. He had also a little jaundice. So we subjected him to a cholecystogram and found he had gallstones. That gave me another opportunity to go into his abdomen, which I did, removing his gallbladder and, incidentally, took the opportunity to examine the site of the operation. It was absolutely free of recurrence of the tumor, and that was two years ago. He was in the office last week and he had no signs whatever of recurrence.

DR. J. SHELTON HORSLEY (Richmond, Va.): I wish to report two cases of leiomyosarcoma of the stomach and a case of neurofibroma of the mesocolon. It is possible that they may be very cellular myomatosis but the number of active cells in many of the sections and the mitotic figures would seem to indicate a low-grade leiomyosarcoma in the tumors of the stomach.

**Case 1.**—W. T. C., white, female, age 62, married, was admitted to the hospital, August 6, 1937. For several days she had been bothered with a cough and a feeling of tightness in her chest. She had been gradually losing appetite and weight for the past six months. There was no history of bleeding from the stomach or bowel, and no nausea or vomiting or any unusual gastric complaint. Her weight upon admission was 115 pounds. There was a mass in the upper left abdomen involving the stomach. There was a large quantity of fluid in the right pleural cavity, from which 800 cc. of clear yellow fluid was aspirated.

**Operations.**—Five days after admission she was operated upon under local anesthesia, and a large tumor was found which involved much of the lesser curvature of the stomach. The liver seemed normal. The pyloric end of the stomach was not involved, and a mid-gastric or "sleeve" resection was performed, though this type of operation does not usually give good functional results. Recovery was satisfactory except that the stomach did not empty well for several weeks. The pleurisy cleared up after a few aspirations. The patient was seen about two weeks ago and was apparently free from any recurrence.

**Pathologic Examination.**—*Gross:* The specimen consists of the midportion of the stomach and the attached tumor, involving much of the lesser curvature of the stomach. It is bosselated, and the protrusions are smooth. Some portions are yellow and others are darker in color. The tumor measures 14x9x7 cm. The segment of the stomach removed measures 12 cm. along the lesser curvature and 18 cm. along the greater curvature. The cardiac end is smaller than the distal end. The mucosa seems to be about normal, though there are a few punctate erosions along the lesser curvature. The mucosa moves smoothly over the wall of the stomach. On section the tumor is solid but is soft with various nodules on the cut surface. They seem to consist of soft granular tissue divided into lobules. The tumor apparently sprang from the muscular coat of the stomach along the lesser curvature.

There is no history to indicate how long the growth had been present, though the patient is a very intelligent woman, and it is probable that it was not palpable very long before she noticed it.

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*Histologic Examination* shows small spindle-shaped cells that are fairly active. There are mitotic figures. From the apparently rapid growth and the activity of the cells it appears to be doubtless malignant, probably a Grade I leiomyosarcoma.

Meigs (Meigs, Joe Vincent: Fibroma of the Ovary with Ascites and Hydrothorax. *ANNALS OF SURGERY*, 110, 731, October, 1939) and others have called attention to the association of hydrothorax with fibroma of the ovary. It may be that in this instance there was an association of hydrothorax with the tumor of the stomach.

**Case 2.**—A. P. B., white, female, age 48, had, for several years, noticed a mass in the abdomen. It had only recently become tender. On admission to the hospital, August 7, 1938, it appeared to be about the size of a large grapefruit. The patient had had six children, the youngest being ten years old; there had been two miscarriages. An ovarian cyst had been removed a good many years ago. The tumor was slightly movable and rather soft. Roentgenologic examination of the gastro-intestinal tract was negative except for showing pressure deformity of the greater curvature of the stomach. It was thought that there was a mass in the abdomen which also displaced the colon.

*Operation.*—August 12, 1938: Under ethylene anesthesia. There was a considerable amount of clear fluid in the abdominal cavity. The tumor sprang from the posterior wall of the stomach by a broad pedicle. It was easily removed. The mucosa of the stomach was not involved. The patient made a satisfactory recovery.

*Pathologic Examination.*—*Gross:* The tumor measures 15x11.5x12 cm. It is oval in shape and of irregular contour. Part of it appears to be soft, as though it contained fluid. The pedicle was from the stomach and contained a section of all of the wall of the stomach except the mucosa. On section, there is a necrotic area with some hemorrhagic exudate, but most of the cut surface is divided into lobules and lobes, as a myoma. There is an area in which there appears to be degeneration, and the tissue is soft and loose, being apparently attached only at one margin.

*Histologically,* the tumor shows spindle-shaped cells with smooth muscle; they are quite active, with a few mitotic figures present. In some areas there is degeneration, probably from interference with the circulation.

Speaking of leiomyosarcoma of the stomach, Ewing says (Ewing, James: *Neoplastic Diseases*, 3rd ed., 278, W. B. Saunders Co., Philadelphia): "The structure varies between considerable limits. In some cases the type approaches that of a cellular myoma, and the recognition of a myogenous origin is readily accomplished. Or the cells are of large spindle form, and the designation as a myosarcoma depends on the attitude of the observer."

The following is a case of neurofibroma:

**Case Report.**—K. W., white, female, age 39, had been having tarry stools for many weeks. She had vomited off and on when she was on a milk diet, but did not vomit blood. She was anemic; her hemoglobin was 42 per cent; red cell count 2,560,000; and white cells 4,200.

The physical examination was essentially negative except for a scar in the lower right abdomen where the appendix had been removed a good many years ago. Roentgenologic examination was negative. She had not vomited during the two weeks before admission. She suffered no pain, but had been weak and anemic for four or five years and recently this condition had increased. The tentative diagnosis was duodenal ulcer.

*Operation.*—February 20, 1928: The stomach and duodenum appeared normal. In the hepatic flexure of the transverse colon was a flat mass arising from the transverse mesocolon and attached to the jejunum. It was extremely vascular. A part of the jejunum and a segment of the transverse colon were resected. The tumor proved to be a degenerating neurofibroma arising from the transverse mesocolon and invading the



upper jejunum at one point. It was at this point in the jejunum from which the hemorrhage occurred.

The patient made a satisfactory recovery, and when heard from recently was quite well.

Histologic examination showed an unusual type of tumor. Dr. A. C. Broders, of the Mayo Clinic, reported, March 5, 1928, as follows: "I am of the opinion that this tumor is a degenerating neurofibroma. I have never seen one in this region, but it has a microscopic picture characteristic of those found elsewhere."

DR. FRANK H. LAHEY (Boston, Mass., in closing): It is interesting that these two types of benign gastric lesions could be discussed here. It is valuable to call attention to these groups. I neglected, or did not have time, to state there had been no recurrence in the follow-up, and this is a very hopeful type of case.

Doctor Cave suggested that I should say just a word about something of the anesthetic management of the gastrectomies and total gastrectomies because it involves differences of opinion. It also brings up a point which I think we should all have in mind, and that is the use of spinal anesthesia. Now, I do not want to debate that question because I know how very controversial it is, but certainly it has made the operation very much easier for us. Because we have had the opportunity in a limited number of cases, now about 31 or 32, to employ this new type of continuous spinal anesthesia advocated by Doctor Lemmon of Philadelphia, I would like to speak about it.

When this method first was suggested to us by Doctor Lemmon, I had a considerable prejudice against it and I think it is but fair to state that that was my position. I felt that permitting an indwelling needle to remain within the spinal canal during an operation was undesirable. I feel that to repeatedly introduce anesthetic solution into the spinal canal during an operation was also unsatisfactory. It is but fair to say, however, that after sending an anesthetist to Philadelphia to learn the method, its employment, in even a limited number of cases, has been entirely satisfactory. I would certainly suggest in the light of our experience up to the present that you do not make the mistake that I made in my prejudice against it. If it continues to give the results that our experience and Doctor Lemmon's up to the present promises, it fulfills many of the requirements for spinal anesthesia that are so desired. It permits the introduction of a small dose, the production of a short anesthesia which can be added to as is required and prolonged with repeated doses up to any extent. There have been no neurologic complications. In the past, one of the most undesirable features of spinal anesthesia over long periods of time has been the large amount of anesthetic agent which had to be introduced so that the length of anesthesia was established no matter what fraction of it was used.

DR. HENRY K. RANSOM (Ann Arbor, Mich., closing): I am glad that this paper on a rather unusual subject has stimulated such an interesting discussion. The two types of tumor under consideration, i.e., those arising from nerve sheaths and those arising from smooth muscle, are in fact very similar, and often distinguished from one another only by special studies and even then at times with considerable difficulty. This distinction between the benign nerve sheath tumors and the leiomyomas, as well as their malignant counterparts, is largely one of academic interest, since from the standpoint of symptomatology, roentgenologic findings, and surgical treatment, they are the same. Since the prognosis is relatively good, an effort should be made to recognize such tumors at an early date, and even though radical operations are required for their removal, the results justify such procedures.



## ILEOSTOMY\*

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AND

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DURING the past decade considerable interest has been aroused in the surgical treatment of ulcerative colitis. Ileostomy, as the first stage in the removal of the colon as well as a complete method in itself to effect "cure," merits discussion. Appendicostomy, cecostomy and, except for certain cases, colostomy have been discarded as ineffectual surgical measures, and have in the past and do at present complicate further surgery when undertaken. Ileostomy deserves no such fate.

Realizing the magnitude of subtotal colectomy with subsequent removal of the rectum, the question has repeatedly been asked, Will ileostomy alone cure this disease? There are those<sup>1, 2, 3</sup> who have felt if ileostomy is performed early enough in the course of the disease no further operative interference is needed and the ileostomy can be closed when the process has healed. Others<sup>4, 5, 6, 7</sup> are of the opinion that ileostomy alone is seldom curative and, except in rare instances, should remain permanent.

This presentation will submit data concerning the indications for ileostomy—the preoperative medical preparation; the immediate preoperative surgical preparation; the technic of ileostomy; the postoperative management as to diet; the care of ileostomy; and the complications and the mortality. Also, the results of a questionnaire sent to members of three national surgical associations<sup>8</sup> will be given, as well as experiences with ileostomy at the Roosevelt Hospital, New York.

At the outset, it is well to emphasize the importance of complete medical control of both preoperative and postoperative periods, and throughout the illness of these patients. Let the physician and surgeon jointly decide the time for surgical intervention and, further, the follow-up should be carefully observed by both physician and surgeon.

*Indications for Ileostomy.*—To subject an individual to ileostomy which, in all but a small percentage, is permanent requires cautious reflection. In the small group of about 10 per cent, where the rectum is free of the disease, ileosigmoidostomy is eminently suited; and in an equally small group, where the disease is proven limited to the left colon, colostomy, relatively easily managed, suffices.

The conditions requiring ileostomy may be classified under two headings: (1) Emergency; (2) elective.

*Emergency.*—In the emergency group impending perforation often necessitates immediate intervention. Heretofore, massive hemorrhage has been

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\* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

considered an indication for emergency ileostomy. Realizing by past experiences that ileostomy, performed at or immediately following massive hemorrhage, is almost always fatal, and that vitamins K and C have been a competent factor in controlling bleeding, we discard this from the lists of indications.

*Elective.*—More numerous are the patients in whom elective surgery can be planned. A previous report from the Gray Service of the Roosevelt Hospital<sup>10</sup> pointed out that the medical prognosis in the individual case depends upon the extent of irreparable damage to the colon and the identification and control of factors contributing to activity of the disease.

In certain instances despite advanced and permanent organic changes in the colon, evaluation and control of these factors permits the individual to remain largely, if not completely, symptom free under ordinary conditions of life or activity. Such individuals necessarily must be classed as instances of satisfactory response to medical care. Surgical intervention is not indicated.

Others, despite repeated investigation and reevaluation, present progressive extension of the pathologic changes and are continuously handicapped by chronic symptoms of greater or lesser severity. Still another group continues to exhibit the characteristic periods of activity and remissions, accompanied by an extending involvement of the colon, and are seriously handicapped by their disease. Surgery must be considered for these two groups.

The results of elective surgery will depend upon two basic factors: (1) Technical procedures; (2) the preoperative and postoperative care. This implies and actually necessitates continuous cooperation by the surgeon and the internist.

*Preoperative Medical Study and Preparation.*—Adequate preparation for surgery demands meticulous, detailed, and prolonged medical investigation of the patient, in some instances as long as one year. Many abnormal conditions which should be corrected among them are: (1) Active food allergy. (2) Disturbed physiology of other parts of the digestive tract (gastric acidity produces diarrhea and flatulence; hypomotility of the colon with right-sided retention contributes to the degree of pain). (3) Psychic and emotional factors. (4) Conventional diets too low in proteins; thiamine chloride; vitamins A, C, D; and certain members of the B complex. (5) Anemias—hypochromatic and microcytic, at times hyperchromatic and macrocytic. (6) Disturbances of mineral metabolism involving particularly calcium, phosphorus and sodium chloride. (7) General malnutrition and inanition.

*Anesthesia.*—We have, in over one-half of the cases, used avertin, gas, oxygen and ether. Lately, however, we have used novocain, procaine hydrochloride and pontocaine, in small amounts, administered low in the canal, as a prolonged anesthesia is not necessary in carrying out this procedure.

*Immediate Preoperative Surgical Preparation.*—Immediate preoperative surgical preparation consists, principally, in thoroughly cleansing the colon by the use of daily irrigations with warm saline solution. It is important

that the fluid balance and the blood chemistry be regulated by the administration of infusions and, if necessary, transfusions. Recently, it has been shown that before and after surgical procedures, the vitamins, especially vitamin C, are markedly reduced; therefore, vitamin supplements are administered sufficiently to saturate the patient.

A nonresidue diet is advisable for 36 hours prior to proposed operation, and lead and opium pills and paregoric render the bowel quiescent.

*Technic of Ileostomy.*—Ileostomy as a surgical procedure has been known for 150 years.<sup>10</sup> It was not, however, until 1913 that John Young Brown<sup>11</sup> made use of this procedure in ulcerative colitis. Since then various modifications of the Brown ileostomy have been employed. One of us (H. W. C.) for the past two years, has employed a form of ileostomy which has proved satisfactory.

A modified McBurney incision is made well away from the anterior superior spine (Fig. 1). The peritoneum is opened. The terminal ileum is carefully inspected (in about 25 per cent of the cases it was found that the terminal ileum appeared reddened, edematous and rigid, yet when reexamined at the stage of subtotal colectomy, only in four instances was it actually involved). We lay great stress about the advisability of not exploring the surrounding peritoneal cavity, at this time; for the reason that disaster has come of this. The wall of the cecum is thinned out. In places it is diseased and it is easy to perforate the cecal wall with the examining finger if great care is not taken. Garlock<sup>12</sup> cites one experience when, inadvertently, he pushed his examining finger through the diseased wall of the cecum.

The exact site of division of the ileum depends upon the amount of inflammatory process which is found to be present, and upon previous roentgenologic studies. Usually six to eight inches from the ileocecal valve, the small bowel will be found to be normal. Two fasciades of vessels in the mesentery are then divided for about three inches. It is, at this point, judicious to see that the ileocolic artery has not been injured. A small stab wound is then made one and one-half inches below the umbilicus, just to the left of the midline. This is to be the site of the distal divided end of the ileum, which becomes a mucous fistula. One purpose of placing this mucous fistula at this point is that at the second stage, when the entire colon is removed, this mucous fistula is in the line of the long, left, paramedian incision. Certainly, the most difficult part of subtotal colectomy is the division of the splenophrenic-colic ligament and it is for this reason that a long incision on the left side of the abdomen is preferable, so that this step of cutting the splenophrenic-colic ligament is made easier.

An Ochsner clamp is introduced through the stab wound below the umbilicus on the left side and is placed to the distal side, where division of the ileum is to be made. A Kocher clamp is introduced through the McBurney incision and this grasps the proximal portion of the ileum. The ileum is then divided transversely with the cautery or a carbolized knife (Fig. 2). The distal end of the divided ileum is then drawn out as a mucous fistula

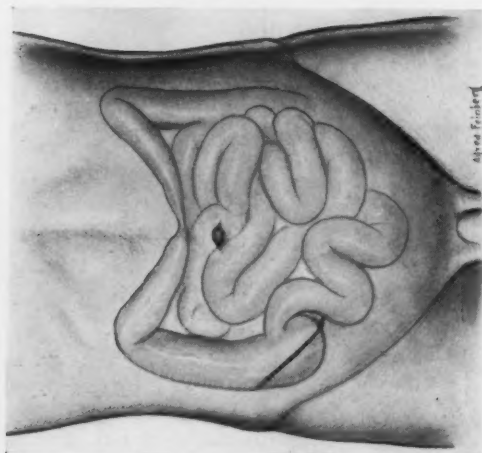


FIG. 1.—Diagrammatically representing a potential stricture in the transverse colon. McBurney incision, the lower angle curved well to the left. The entire incision should be well away from the anterior superior spine to permit the comfortable use of a bag.

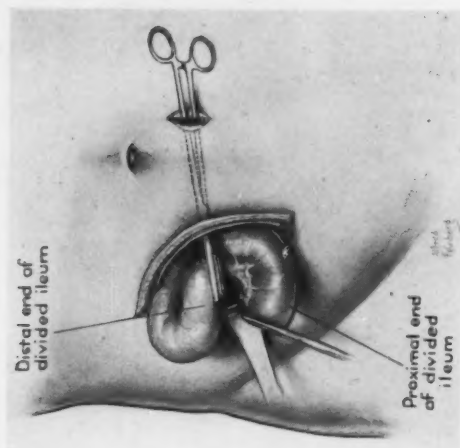


FIG. 2.—Distal divided end of ileum to be drawn through stab wound to left of midline. Proximal end brought out at lower angle of modified McBurney incision to constitute the permanent ileostomy opening.

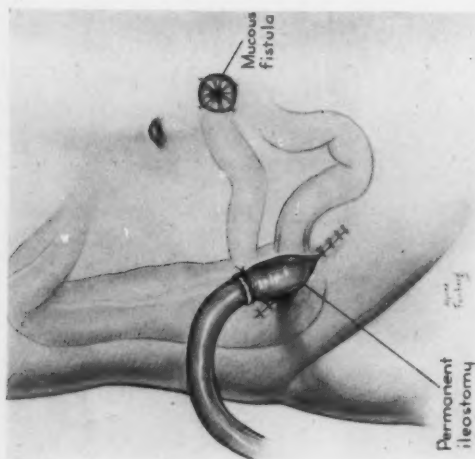


FIG. 3.—The permanent ileostomy with large caliber rubber tube in position. Also, showing a suitable site for the mucous fistula.

through the stab wound, to the left of the midline, and a few sutures are taken in the mesentery to prevent retraction (Fig. 3).

The proximal end of the ileum is then brought out through the lower angle of the McBurney incision; in fact, of late, we have found it preferable to divide the fascia over the rectus muscle, push the rectus muscle medialward, if necessary divide its outer fibers, thus being assured that the ileostomy will be toward the midline and well away from the anterior superior spine. In order to prevent loops of small intestine from prolapsing through the rent in the mesentery, and also in an effort to prevent the ileostomy from prolapsing, interrupted sutures attach the cut end of the mesentery to the peritoneum well underneath, and to the fascia. The wound is now closed in layers about the protruding ileum (Fig. 3).

Two inches of ileum should protrude from the anterior abdominal wall. The clamp is immediately removed from the protruding proximal ileum and a good-sized rubber tube is placed into the stoma and carefully tied with a segment of cotton tape. A greased gauze dressing is applied.

The tube connects with a bottle over the side of the bed and usually within 24 hours it begins to function. The tube usually remains secure in the ileum for about eight days, at which time it drops out and the contents of the ileum pour out on the anterior abdominal wall. Caution should be exercised to eliminate any excoriation of the skin.

We have found this best prevented by the use of: First, applying compound tincture of benzoin, over this is sprinkled Fullers' earth, and a salve made of aluminum powder; cod liver oil and zinc oxide are frequently used. From the beginning, the patient is instructed to look after his own ileostomy. Pledgets of cotton are supplied to him in abundance so that the discharge may be wiped away at frequent intervals.

*Postoperative Management.*—Immediately following ileostomy, a transfusion is administered. In order to insure the immediate functioning of the small bowel through the newly made ileostomy stoma, adequate fluids, by venoclysis, or Hartman's solution and 5 per cent glucose in saline are administered.

Serum protein, the chlorides and calcium content of the blood are carefully checked at intervals following operation. Determination of plasma and serum specific gravity is also of value in aiding the maintenance of chemical balance. If there is found to be a deficiency in vitamins K and C or if a raised prothrombin time is present, these vitamins are given. Thiamine chloride 25 mg. is given intramuscularly for three days prior to operation and for the first ten days postoperatively. This vitamin assures an improved appetite and aids materially in coaxing these patients to begin eating early following the operation and maintains the desire for food. This factor is important in the restoration of function of the ileal stoma.

The day of the operation, the patient is urged to chew gum and is given cracked ice. For the first day postoperative, soda crackers and melba toast with cracked ice are alternated every two hours with orange or lemon juice



until the ileostomy drainage begins. A soft, low residue diet is given in the afternoon as small feedings every three hours. The second day postoperative, the soft diet is continued as six feedings with copious amounts of fluids. On the third day after operation, a more solid diet is permitted. This diet is continued until the tube drops out, usually from the eighth to the tenth day, when a regular diet is instituted, unless food idiosyncrasy is known to be present.

In those patients where the serum protein tends to be low in spite of transfusions, a high protein, high carbohydrate diet is advisable.

The following beneficial results are enumerated: (1) The ileal stoma functions usually within 24 hours. (2) There is a minimum amount of postoperative gas and distention; thus the risk of vomiting and ileus is minimized. (3) The sense of well-being is rapidly restored. (4) The weight is maintained, so that usually the convalescent weight loss is seldom more than three to five pounds.

*Complications of Ileostomy.*—The complications of ileostomy, often annoying, are seldom fatal. Bleeding from the mucous membrane lining the stoma is occasionally thought by the patient to be involvement of the small bowel. In one instance bleeding so severe occurred that adrenalin and pressure bandages had to be resorted to.

Prolapse of the ileum is not uncommon in the earlier cases in our series before suture of the ileal mesentery to the fascia was carried out. Many prolapsed; several protruded four to six inches from the surface of the anterior abdominal wall, and still do. As yet, in no instance have we had to revise an ileostomy for this reason.

Retraction of the stoma from the abdominal wall may occur, especially in fat individuals where it has proved difficult to estimate the proper amount to withdraw from the abdomen. Careful fixation of the mesentery to the fascia will prevent this.

In three instances, narrowing of the stoma with impending stricture has resulted from too close suturing of fascia about the bowel. This we have overcome by repeated daily dilatations by the patient's index or little finger.

A poorly selected site for the ileal stoma in our one experience (too near the anterior superior spine) necessitated an additional operation in order to transplant the opening nearer the midline of the abdomen.

Due to an ill-advised suture in the ileal wall itself, secondary openings proximal to the stoma developed, in two of our patients, necessitating revisions in both instances.

Intestinal obstruction, particularly of loops of the small intestine, is a complication to be dreaded. One of the patients in our series suffered from acute ileus on two different occasions. Enterostomy fortunately relieved the first obstruction; removal of the ileostomy stoma to the left side of the abdomen was deemed necessary following the second episode, and subsequently proved to be justified. Two other individuals were temporarily blocked, were hospitalized and were relieved by palliative measures.

# ILEOSTOMY

An unusually striking sequela of ileostomy was repeated attacks of pronounced collapse due to the loss of NaCl from the sudden and rapid ejection of fluid from the ileostomy stoma. This patient was so debilitated that he has returned to the hospital upon three occasions seeking intravenous administration of fluids and chlorides.

*Results of Questionnaire.*—The answers to our questionnaire revealed noteworthy information. We were particularly interested to learn: First, if patients had been cured by ileostomy alone; and second, whether subsequent closure of ileostomy had been justified.

TABLE I  
Ileostomy Without Closure

No. of Patients	
77	Results not given
26	Results given:
	13 of these 26 . . . . . were symptom-free; a few "cured"
	13 of these 26 . . . . . symptoms continued
51	Deaths, or mortality of 33%
<hr/>	
Total	154

With the results given in only 26, excluding deaths, no conclusions can be drawn as the number is too small. It was of interest to note that in two patients the disease progressed beyond the ileostomy into the adjacent proximal loop, reemphasizing the now indisputable value of transverse or single barrel over loop ileostomy. However, the mortality following ileostomy of this group of 154 patients was 33 per cent, which is not unexpected considering the published reports of various other surgeons. This mortality impresses one with the seriousness of ileostomy. The principal reason for the mortality in many instances is that surgical aid is frequently sought too late. The acute, fulminating group with actual or impending perforation, massive hemorrhage, or chronic intractable patients who have been debilitated to a marked degree and who have been inadequately treated medically, are bad surgical risks. Admittedly, ileostomy is not a difficult technical procedure; it was, in the past, attended by a considerable mortality. Cattell's<sup>13</sup> mortality of 22 per cent; Kunath's<sup>14</sup> 83 per cent mortality following ileostomy in 12 patients, and our total mortality of 23 per cent, all emphasize the necessity of earlier surgical intervention and better preparation for operation. In certain individuals, thorough medical study and careful postoperative care are essential. In no small measure has the high mortality been due to a rapid and excessive loss of fluid and chlorides immediately after operation.

Of this small group who were subsequently closed, 59 per cent were restored to health, for an average of nine years. This is encouraging, yet from the answers it was difficult to conjecture the degree and the extent of the pathologic process prior to the preliminary ileostomy.

The shortest elapsed interval between establishment of ileostomy and closure was two months, the longest approximately seven years. The op-

timum time for closure (if they are to be closed) does not depend on the interval between the establishment of ileostomy and its closure, as on the condition of the bowel and extent of the colonic lesion as determined by roentgenologic and proctoscopic examinations and the clinical signs and symptoms.

TABLE II

No. of Patients	Ileostomy with Subsequent Closure
22 or 59%	Restored to health. Follow-up 2-20 yrs. (average 9 yrs.)
9 or 25%	Recurred:
	1—Nothing done
	3—Reoperated upon: Second ileostomy necessary (2 of these symptom-free. 1 not improved)
	5—Not stated what was done

## Mortality in Those Closed

## 6 Deaths, or 16.7%:

- 1 Died 1 mo. later—leakage at site of anastomosis (ileosigmoidostomy)
- 1 Died 2 yrs. later—recurrence
- 1 Died 8 yrs. later—recurrence
- 3 Cause of death not stated

Nine of these patients showed a recurrence of their disease following closure; three were operated upon and second ileostomies were found to be necessary. It is our opinion that it is a rare experience to successfully close an ileostomy in ulcerative colitis when the colon shows extensive ulceration, fibrous or pseudopolypoid degeneration. Garlock,<sup>15</sup> of the Mt. Sinai Hospital, New York, is strongly in favor of preserving the rectum, in the hope that the process will subside to the point where it will be safe to close the ileal stoma and divert the fecal current through the anal opening by performing an ileoproctostomy. The mortality of 16.7 per cent, or even higher death rate, can be expected not only from technical risks but from late recurrence. Mackie's<sup>16</sup> contention is endorsed, that: "It is impossible to say that after any given period of freedom from activity the disease will not recur."

From replies received, but few of the patients fell into the acute, fulminating group, and it was evident that the majority of procedures carried out were of an elective nature.

## EXPERIENCE WITH ILEOSTOMIES

## FROM THE

## GRAY SERVICE AT THE ROOSEVELT HOSPITAL

Three hundred five patients suffering from ulcerative colitis have been treated on the Gray Service at the Roosevelt Hospital during the last four years. Of these, 45 have been subjected to some surgical procedure. Sixty-nine maneuvers have been carried out on these 45 individuals. Of these, 30 have been ileostomies. There were 23 males and seven females. The

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average age of these 30 patients was 29.8 years. The average duration of symptoms was seven years; the shortest illness recorded was two weeks and the longest was 25 years. It was of interest to note the status of these individuals when they came to surgery. Eight were subjected to operative interference on account of perforation, two on account of hemorrhage, three on account of obstruction and 17 because they were suffering from the disease in a chronic intractable form.

TABLE III  
STATISTICAL RÉSUMÉ OF ILEOSTOMY DEATHS

		No. of Cases	Deaths	Mortality
Ileostomies:		30	7	23%
Emergency ileostomies.....		11	5	45%
Elective ileostomies.....		19	2	11%
Patient	Type	Cause of Death		Death
1. S. B. ....	Emergency	Inanition.		
		Vitamin K deficiency		Medical
2. F. G. ....	Elective	Peritonitis		Surgical
3. F. K. ....	Emergency	Peritonitis		Surgical
4. G. S. ....	Emergency	Massive hemorrhage		Surgical
5. C. D. R. ....	Emergency	Peritonitis		Surgical
6. J. N. ....	Emergency	Paralytic ileus.		
		Hemorrhage		Surgical
7. W. E. ....	Elective	Embolism		Surgical
8. D. R. ....	Emergency	Peritonitis		Surgical

The extent of the pathologic lesion, as presented, showed: Extensive ulceration in 17; fibrosis and shortening in 16; and pseudopolypoid degeneration in 12. In our experience with the earlier cases, we made a practice of suturing the distal divided end of the ileum and dropping it back in the peritoneal cavity. Realizing that a certain number of these cases would go for a long period of time before being subjected to subtotal colectomy; and due to a stricture with a subsequent blow out of a sutured distal end, it is brought out as a mucous fistula. One might well say that this was not necessary if careful roentgenologic study was made prior to ileostomy, in order to determine the presence or absence of an impending contracture. Cattell<sup>17</sup> states: "My decision not to drop back the ileum was based on the observation of marked contractures developed in the colon after ileostomy."

The most striking feature of our experience in this disease has been a rapid gain in the vast majority of these patients after ileostomy. The average weight gained in 16 of our 30 patients was 27 pounds. The average length of time in which the weight was gained was five and one-half months.

Of the total ileostomies, there were seven deaths, or a mortality of 23 per cent. In discussing the mortality statistics of our ileostomies, we have divided them into "emergency" and "elective" ileostomies. There were 11 emergency ileostomies with five deaths, or a 45 per cent mortality. Of the

elective ileostomies, there were 19, with two deaths, a mortality of 11 per cent. Of the two deaths in the elective group, one died of peritonitis due to embarrassment of the circulation of the bowel wall, a technical surgical error; the second succumbed of an embolus six days after operation. Of those in the emergency group that succumbed, three died of peritonitis and two died of hemorrhage. We are fearful of performing ileostomy upon patients in the presence of massive hemorrhages.

We did not assume that ileostomy alone or ileostomy with reestablishment of the fecal stream could have proven curative in any of the 30 patients reported from the Roosevelt Hospital Series, and was performed solely as a preliminary step to the radical removal of the diseased colon and rectum.

There is an amazing psychologic improvement in patients who have submitted to ileostomy, principally, we believe, because they realize some radical curative measure has been undertaken. Following this procedure, except for a short period postoperative, the patient gains in weight and in strength. The ileal stoma is occasionally relatively quiet at night, and although they suffer the annoyance of an artificial and misplaced anus, they finally and fully realize that in order to live, they must put up with this inconvenience.

#### CONCLUSIONS

(1) Appendicostomy and cecostomy based upon false premises (irrigating the colon with antiseptic solutions, in the hope of destroying invading organisms and thus effecting a cure) are discarded as useless.

(2) Indications for surgery:

- A. Impending perforation.
- B. Progressive extension of pathologic lesion; patients continuously handicapped by the disease.
- C. Patients exhibiting periods of activity and remissions destroying their usefulness.

(3) Detailed and usually prolonged medical supervision should adjust the following disturbances:

- A. Active food allergy.
- B. Altered physiology of other parts of the digestive tract.
- C. Psychic and emotional factors.
- D. Avitaminosis.
- E. Anemias.
- F. Mineral metabolism involving particularly calcium, phosphorus and sodium chloride.
- G. General malnutrition and inanition.

(4) Prior to operation the fluid balance and blood chemistry are adjusted. Vitamin supplements are administered to maintain proper vitamin levels. A nonresidue diet diminishes the presence of small intestinal contents at the time of operation.

(5) A general and a small amount of spinal anesthesia are equally sufficient.



## ILEOSTOMY

- (6) The steps of a new ileostomy are outlined.
- (7) The feeding of dry foods, followed almost immediately by a regular diet, insures a minimal amount of gastric distention and forcible peristalsis; results in early functioning of the ileal stoma.
- (8) The deductions from a questionnaire reveal that:
  - A. Ileostomy is rarely a curative procedure in ulcerative colitis.
  - B. In very rare instances, the continuity of the gastro-intestinal tract may be successfully reestablished.
- (9) Ileostomy is, in the majority of instances, primarily carried out as the first step in the complete removal of the colon and rectum.
- (10) At present, the mortality following ileostomy in the emergency group of our series was 45 per cent; however, in the elective group it was only 11 per cent.

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DISCUSSION.—DR. HARVEY B. STONE (Baltimore, Md.): One may divide the cases upon whom ileostomy has been performed for the treatment of ulcerative colitis into three groups, dependent upon their subsequent course following ileostomy: There is a small group that fail to improve either in their general condition or in the local disease in the bowel. On the contrary, they get worse. That group to which Doctor Cave has given a great deal of attention in his own work, although he did not emphasize it in the paper, probably are best treated by stage-colectomies. A much larger group improve materially in their general condition. They gain weight. They gain strength. Their blood count comes back to normal. Their temperature returns to normal. They regain their working efficiency but the disease in the bowel, although static, is not cured. That is the group about which the late Dan Jones used to say that ileostomy cures the patient but it does not cure the disease, and of the total group of ileostomy cases, this group, I think, is by far the most numerous.

Then there is a third smaller group who do recover, not only insofar as their general welfare is concerned, but the disease heals, consequent to the rest afforded the colon as a result of the ileostomy; and in these people the ileostomy may be closed and the alimentary tract restored to normal. I realize that there are many men, some of them quite experienced, who will deny the existence of such a group of cases—but there is such a group! It has been incontrovertibly proved by experience and, as a matter of fact, the statistics which Doctor Cave has just shown us reveal that in, I think, 37 cases of his total series closure was effected, and only 25 per cent of those closed had subsequent trouble. So that there is a group in which permanent definitive cure may be expected. It seems to me that the problem of the treatment of this disease should focus upon enlarging this group of cases at the expense of the other two groups, so that we may get more people in whom ileostomy can produce a definitive cure, and, to do this, it seems to me it is essential that the treatment be invoked before irreversible changes have taken place in the large bowel. I cannot see that there is much hope for a permanent cure after the disease process has extended into the wall of the bowel, under the mucosa, and converted the colon into a rigid, fibrous tube; therefore, I think that we should urge operation before these irreversible changes have taken place.

I believe there is at least a criterion which might be employed to decide when to advise ileostomy. In the past, I think it has been the custom to advise ileostomy on the basis of the two suggestions made by Doctor Cave: The progressively uninterrupted progress of the disease downward, what he calls his grave, continuous cases; or the intermittent but constantly recurrent group of cases. I would suggest that another test be applied in advising ileostomy, namely, the discovery, by repeated roentgenologic examination, of the beginning of permanent change in the large bowel. When the radiologist reports that all the haustration is disappearing from the colon and that, on fluoroscopic examination, it is beginning to lose its flexibility, you have there evidence of the initiation of irreversible changes; and that is the time to employ ileostomy before those changes have gone any further.

Why do we not do this? Well, I think there are two reasons: In the first place, clinically, many of these patients, even after having been ill a good while, enjoy a period, at least, of recovery, and the doctor and patient constantly hope that this individual case will, tomorrow or next week or some time soon, have a recovery which may be permanent, so that the constant hope of spontaneous or medical cure defers operation. I suggest that if roentgenologic examination shows changes in the organic structure of the colon, that hope be abandoned. The second reason ileostomy is deferred is because of the extremely disagreeable nature of the treatment. As a matter of fact, I think many people feel that the treatment is worse than the disease. It occurs to me that that is a challenge to surgery, to our technical mastery of this problem, to see whether there may not be some method by which a better type of ileostomy can be performed to diminish the disagreeable features consequent upon its performance.

(The speaker here demonstrated by lantern slides a procedure which he had employed in three cases.) After the ileostomy had been established, an incision was made mesially to it. A loop of ileum immediately above the stoma was drawn out, its two arms sewn together by a posterior suture, an incision made, similar to that of a Finney pyloroplasty, between the two arms, and the anterior suture completed. This resulted in the production of a loop that was self-anastomosed, and which formed a collecting reservoir immediately proximal to the position of the stoma.

## ILEOSTOMY

This procedure was undertaken in the first instance to correct a very annoying, long prolapse through the ileostomy stoma. It did that efficiently, but it also considerably slowed up the number of discharges from the stoma, led to a considerable absorption of fluid and a thicker consistency of the material discharged. So that I have employed this procedure in two other cases, in the hope that this might improve the status of these people who have an ileostomy. This point in operative technic is merely offered as a first suggestion of an attack upon the problem of ileostomy, in order that it may be made a more tolerable condition and, therefore, reduce the reluctance of doctors and patients to subject patients to this form of treatment.

How can one tell when a patient, who has had an ileostomy performed, is a fit subject for closure of the stoma? Well, in addition to all the well-recognized tests, recovery from his illness, restoration to weight, blood count, *etc.*, in addition to a proctoscopic examination which shows a normal mucous membrane in the rectum and lower sigmoid and to roentgenologic study of the higher portions of the colon, I would suggest one further test: If a patient, otherwise apparently ready for closure of the stoma, has his colon injected per rectum with two liters of normal salt solution, the fluid retained a little while and then expelled, collected, centrifuged, and the precipitate examined microscopically for red cells and leukocytes, and none such found, I believe that one can then safely close the stoma.

DR. FREDERIC W. BANCROFT (New York, N. Y.): I should like to discuss the third group that Doctor Stone referred to—the group where the ileostomy may possibly be closed. I have closed four. One caused a very sudden recrudescence of the disease, resulting in mortality. One, I followed for one year, and was well when last seen; one, for four years, who was still well. I should like to give an eight-year-old history in lantern slides, if I may, of a man whom I operated upon in 1932. (Doctor Bancroft here showed lantern slides of the condition of the man before operation, and then following his ileostomy in 1933.)

A barium enema study was made in 1934, at which time the patient was seen by Doctor Stone, who sigmoidoscoped him; and we thought we were safe in reimplanting the ileum. This operation was performed, in 1934, by transplanting the ileum into the transverse colon. He was well for about one year, and then had a recrudescence of his diarrhea after chopping wood, fishing and paddling a boat, so that, in 1935, the cecum and ascending colon were resected as far as the anastomosis. Since that time, he has been very well; has been able to carry on his business; and has been very active in fishing, hunting, climbing and golfing. Barium enemata, in 1936, 1937 and 1939, showed a moderate polypoid formation of the descending colon, which has decreased within the past year, and which shows, very definitely, the disappearance of the pipe-stem appearance of the bowel. It is my impression that this polypoid formation, in some cases, is the result of healing—and not the progress of the disease. It has been now three years since he has had blood in his stool. His only objection to me as a doctor is that I will not let him play 36 holes of golf a day. I have restricted this exercise, as he has a rather weak abdominal wall and I feel that golf may be too much of a thrust on his abdomen.

DR. FRANK H. LAHEY (Boston, Mass.): I think this is an extremely important subject. I feel sure that a great many patients die needlessly every year due to the fact that we do not get the gastro-enterologists and the medical men to cooperate well enough with us about early ileostomies. Those of us who have the good fortune to have gastro-enterologists or medical men

associated with us, can get early ileostomies done because of the fact that we have made our mistakes together, and have learned not to put these cases off until the disease is too advanced. What we need is to get before the medical public the fact that this late delivery of patients with ulcerative colitis, who are candidates for ileostomy, to surgeons, results in most of the mortality of this disease.

We have had to date approximately 300 patients with ulcerative colitis, and it is only by the bitter experience with the results of delay that we have been able to convince even our own gastro-enterologists that these patients should be operated upon earlier. On the other hand, there are some things to be said in the gastro-enterologists' and medical men's favor who delay ileostomy. We must admit it is a very poor type of enterostomy and, no matter what one may say about its necessity, it must be admitted, also, that it is an undesirable type; therefore, no one wants it. It is but natural that the patient and his medical adviser should delay having it undertaken as long as they can. On the other hand, this is an extremely difficult psychologic situation and one, of course, that can and does result in undue delay and at times unnecessary fatalities.

I do not quite agree with Doctor Stone that this early change in the colon should be an indication for ileostomy because we have to admit that there are many patients with fairly rigid-appearing colons who are getting on very well. I wonder if I, myself, might not possibly accept a fairly rigid colon with some hazard rather than an ileostomy. From our experience with those patients who have had ileostomies (70 in number) in our hands and those patients who have not required surgery and who are getting on reasonably well without it (59 per cent of all the cases which we have seen), there are many who have quite rigid colons and who have had fairly rigid colons over a number of years but have still been able to manage without an ileostomy.

We should be careful as to the type of ileostomy which we employ. There is no doubt but that the end-ileostomy, of the divided type which has been described by Doctor Cattell in this clinic, is the best type. But this type requires considerable technical manipulation which in very advanced and toxic cases will undoubtedly result in fatalities which would not occur in less advanced types. It is, therefore, important to divide those cases into the very severely ill who will stand nothing more than the loop-ileostomy, even if it is undesirable, without manipulation of the colon in any way, and those in whom a divided-ileostomy may be performed and so implanted in the abdominal wall that later colectomy can be undertaken without difficulty.

One other point, and that is that everyone who deals with ileostomies will have trouble with them. We have had them prolapse and we have had them pull away; therefore, some time ago, we advocated the suture of the mesentery to the abdominal wall. This is a very important point in preventing prolapse and the pulling away of the ileum in these cases.

One other very important point is that some type of fairly tight suction tube be introduced into the ileostomy immediately after it is made until good wound healing has taken place, because liquid fecal discharge is one of the things that breaks the ileostomy down. Doctor Lium, an exsurgical fellow in our clinic, has devised a type of ileostomy tube which can be inserted into the ileostomy immediately, which will keep it dry while the wound heals soundly, and I think that is an important point.

We have here, I believe, a most difficult situation, and what Doctor Cave has said is extremely important, that is, we will always have difficulty as long as the gastro-enterologists or medical men handle these cases separately, and then turn them over to us as technicians solely to do these things. When they



can see and feel responsible for the undesirable effects of delay, and when even after temporary good results with ileostomy, later recurrence of blood, increased pulse rate and elevated temperature and fatalities also take place as the result of delay, then we will get them to submit their patients to early ileostomy and to early colectomy.

One other thing, and that is you can assure a patient with ileostomy that after you have performed the colectomy the ileostomy will be easier to manage, the number of stools will be less, and the type of discharge will tend to be more solid.

DR. VERNON C. DAVID (Chicago, Ill.): I should like to endorse the early ileostomy; largely from the standpoint of some of the very serious things that happen in delayed ileostomy, and in which serious damage of the bowel has occurred. My experience has differed somewhat from Doctor Bancroft's intimation that polyposis, occurring in chronic ulcerative colitis, is a favorable lesion. We have recently had the opportunity of examining a colon which for many years had been ulcerated in which polyposis had occurred, and contrary to our usual view that these lesions are purely hyperplastic lesions of isolated areas of mucosa which have been preserved between the ulcers, one can trace not only hyperplastic lesions but also can find tumors which in all respects resemble papillomata and adenomata of the colon.

One further remark about the undesirability of having late ileostomy. The disagreeable complication of stricture and thickening of the bowel and the development of polypi has occurred in three of our patients who have developed, after long-standing ulcerative colitis, carcinoma of the colon. We have, at the present moment, a woman in whom, about six months ago, we resected the transverse colon for carcinoma, who now has another carcinoma in the rectum. So that these long-standing ulcerations with polyposis have really serious significance.

DR. EDWIN M. MILLER (Chicago, Ill.): Presented a slide of a child, age seven, with an intractable ulcerative colitis, in whom an ileostomy, after a six-month period of trial, has been eminently successful thus far. After three months on the Medical Service, following an illness of seven months previously, she was referred to us. The ileum, as one can see, was completely divided, and the skin flap brought together between the open ends of the bowel. She has very rapidly picked up physically and mentally, and has become one of the happiest little patients we have in our ward at the County Hospital. There has never been anything applied on the skin to prevent irritation, still the skin has always been in excellent condition. She has spent most of her nights and a part of the time during the day face down upon a frame in which there is an opening, so that the contents of the proximal ileum drains directly into a receptacle, and during the day, at intervals, the nurse irrigates this area with a little sterile water.

I do not know when, if ever, I shall be able to close this ileostomy, but I do have an idea that, after sufficient time has elapsed, I shall try to see what the colon will tolerate, by collecting some of the material from the proximal bowel and introducing it into the colon through a catheter, and having done that, over a sufficiently long time, without having evidence of a flare-up of the active process, I may find that the time will have arrived when we may close the ileostomy permanently.

DR. HENRY W. CAVE (New York, N. Y., closing): I do not agree with Doctor Stone in the question of performing ileostomies early. If an ileostomy is to be established early, the simple method is to bring out a loop of the



terminal ileum, sew the loops together side-to-side, divide the loop, bring out the distal end at one end of the wound and the proximal end at the other end of the wound, as is done in the Devine procedure in the colon. Although I have not employed it, I believe it probably would be a simpler procedure than the one Doctor Stone has suggested. I firmly believe that patients showing early changes in the colon should have a prolonged and adequate medical supervision. Dr. Thomas T. Mackie, Director of the Grey Laboratories for the study of ulcerative colitis at the Roosevelt Hospital, has shown me patients with early changes in their colon that would seem as though they were going on to an irreversible stage. These patients, by medical management, have been cured for periods of seven to eight years. But it seems to me advisable that a conservative attitude should be taken in performing ileostomy too soon.

We have one patient, a male, age 50, whose disease started at the age of 25, and he has had the disease for 25 years. We have roentgenograms showing the start of the disease after 20 years. It was well into his rectum, but it traveled up his ascending colon into the splenic flexure, across his transverse colon and down to his cecum, and his terminal ileum is involved as well. He finally, after having had the disease for 25 years, submitted to ileostomy; and during these 25 years he has enjoyed very good health.

Another patient had an ileostomy performed eight years ago. She got along well, except during the fall, when she suffered from hay fever, at which time she would have profuse bleeding from the rectum. After eight years, she finally submitted to a subtotal colectomy, and since that time has gained 16 pounds in weight. She, apparently, had been absorbing from this diseased colon and it was a menace to her. Therefore, after eight years, we felt that for her to be in better health the diseased viscus should be removed.

Doctor David has commented on the question of the incidence of carcinoma superimposed on chronic ulcerative colitis of the colon. From the literature, more than I can gather, I would say that 3 per cent of the patients who have reached an irreversible stage of pseudopolypoid degeneration will develop cancer.

## THE SURGICAL MANAGEMENT OF CARCINOMA OF THE LEFT HALF OF THE COLON\*

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IN MAKING A STUDY of lesions of the large intestine, we have considered separately those of the right side and those of the left side of the colon. The study of lesions of the right half of the colon was reported recently.<sup>1</sup> Four cases, in which the tumor occurred directly in the midportion of the transverse colon, though analyzed separately, are included in the present study.

Seventy-eight patients with carcinoma of the left half of the colon and transverse colon (exclusive of the rectum) were treated at the University of California Hospital during the last ten years (1930 to 1940). Three of these had a second lesion of the colon, requiring separate resection, bringing the total to 81 cases. Of the 81, 32 received palliative treatment only, and 49 had resections. The operability of the whole series, then, was 60.4 per cent.

All of us realize the necessity for early diagnosis and treatment in dealing with any malignant condition. Failure to detect the disease early in its course may result from ignorance on the part of the patient. Too often it is directly attributable to carelessness on the part of the profession. The old teaching that blood in the stool or a change in bowel-habit means a lesion somewhere in the bowel is just as true as when it was first postulated. Perhaps it is even more important now, for not only have we diagnostic aids at hand, but operative means of relief as well for patients whose diagnosis is made early. It is the physician's responsibility to use every means at his command to find the source of the trouble.

Once the diagnosis is made, preparation for operation becomes of paramount importance. If the patient has an acute obstruction, it is obvious that his symptoms must be relieved at once either by an indwelling nasal tube into the stomach, or by some form of decompressive operation such as cecostomy or colostomy performed under local anesthesia. We prefer a combination of the two. The distention in the large bowel may be so great that there is danger of rupture of the cecum, and cecostomy may be necessary as an emergency measure. For patients who are not suffering from acute obstruction, some controversy exists as to whether or not cecostomy or colostomy should be performed some time before resection is undertaken. Some surgeons remove lesions of the descending colon or sigmoid in one stage, either with a cecostomy or colostomy at the same operation, or without decompressive

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operation of any type. In our opinion, however, resection of any portion of the left side of the colon with a primary anastomosis is very hazardous unless cecostomy or colostomy has been performed previously. Whether a colostomy is to be performed just above the lesion, or in the transverse colon, or a cecostomy is to be established, is a matter of choice for each surgeon. We usually prefer a cecostomy because it is a smaller procedure, it can be performed under local anesthesia, and the wound is easier to close. If properly made, it is adequate for cleansing the bowel before surgery. Our custom is to perform a cecostomy under local anesthesia. During the next ten to 14 days a nonresidue diet high in carbohydrates and vitamins is given, with transfusions of blood as needed to bring the blood picture to normal; daily washing of the bowel through the cecostomy and the rectum is carried out. One ounce of Epsom salts in eight ounces of water is given each morning for several days before the operation. The foregoing procedures allow the infection and edema of the proximal bowel and tumor to subside, thereby making the suturing safer. Two days before surgery, 1 gr. lead and opium pills are given three times a day to reduce the intestinal activity. When possible, these patients are permitted to be up and around rather than at complete rest in bed. Such a regimen brings the patient to the best possible condition before resection is undertaken. The patient who is gaining weight is a much better risk than one who is losing weight, and the time taken for preparation before resection is well spent.

The choice of anesthetic depends on the age, general condition and temperament of the individual patient, as well as on the location of the tumor. Spinal anesthesia is not used for a lesion in the splenic flexure, but is used for lesions lower down. The transverse incision, described by Hoag,<sup>2</sup> is of great advantage in the removal of a tumor of the splenic flexure or the descending colon.

It should be apparent that no single type of operation is applicable to all lesions of the left side of the colon; one of a number of different procedures may be employed according to the necessities of the case. The type of operation chosen depends upon many factors—the age and general condition of the patient, the location and fixation of the tumor and the preference of the individual surgeon. If it is true that the method sometimes depends more upon the preference of the surgeon than upon the other factors, it is equally true that the method is not so important as the man behind it. One surgeon may use clamps for the anastomosis; another may use the open method. Each may be right, depending upon his training and experience. In training a resident staff, however, it is important to teach one method of resection and anastomosis well.

In this group of 49 operations there were 13 Mikulicz procedures, three Rankin obstructive operations, three Hartmann procedures, 22 end-to-end anastomoses, and eight side-to-side anastomoses.

The Mikulicz procedure does not permit the removal of so much lymphatic-bearing tissue as a more extensive resection, and a longer period of time is required for complete closure when this procedure is used. The Hartmann

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operation is employed only when the lesion is so low as to preclude an anastomosis to the short distal stump of bowel which remains, or when the general condition of the patient does not warrant an abdominoperineal resection. This procedure has the advantage that the perineum and the nerve supply to the rectum and bladder are left intact. Rankin's obstructive operation need not be done if a previous colostomy or cecostomy has been performed as indicated above. We prefer to do an anastomosis.

Our choice of operation is resection, after the careful preparation described above, followed, if possible, by either an end-to-end or a side-to-side anastomosis by the open method. In performing the resection, we free the bowel beyond and below the lesion, using as wide a margin as possible and taking a large section of mesentery with the tumor. After the point of transection has been determined, the flow of the fecal stream is controlled by the use of broad rubber bands around the bowel rather than the use of clamps. The blood supply to the large bowel is so precarious that the use of clamps may injure it to the extent of causing thrombosis in the vessels, with delayed healing and even leakage. The bowel is transected with the electrocoagulation unit and, if a side-to-side anastomosis is to be made, the ends are turned in with catgut sutures and reinforced with Halsted mattress sutures. The loops of bowel are then held in approximation by stay sutures of silk and the first posterior row of interrupted silk sutures is placed and tied. The Halsted mattress sutures of silk are laid anteriorly and retracted over the stay sutures. The opening into the bowel is made with the electrocoagulation unit adjusted so that the coagulation will control all bleeding. This prevents contamination of the suture line by blood from the incision into the bowel. Local peritonitis around the line of sutures predisposes to the breakdown of the anastomosis with subsequent leakage, general peritonitis and death. A row of continuous catgut sutures is placed posteriorly, taking the full thickness of the bowel, and is tied. The row of sutures previously laid anteriorly is tied and reinforced with interrupted Lembert sutures of silk. The anastomosis is further protected and walled-off from the small bowel by the omentum. The abdomen is closed without drainage. Essentially the same technic is used if an end-to-end anastomosis is performed.

Five deaths occurred among the 49 patients, a mortality of 10 per cent. This compares favorably with the operative mortality in the 27 lesions of the right side of the colon (Table I). If the 49 operations are divided according to their positions as transverse or left, it is seen that the mortality for lesions on the left side of the colon drops to 8.8 per cent (Table I).

Of the five patients who died, one, a woman, age 47, succumbed suddenly on the seventh day after operation, presumably from pulmonary embolus. This patient had had a cecostomy, followed in eight days by a resection with a side-to-side anastomosis. Her course after operation had been remarkably smooth until the seventh day when, upon turning over in bed, she suddenly died. Unfortunately, autopsy was not permitted, but the clinical picture was that of massive pulmonary embolus.

TABLE I  
COMPARATIVE MORTALITY OF RESECTION OF CARCINOMATA OF THE  
LARGE INTESTINE

	No. of Cases	No. of Deaths	Mortality Percentage
Right colon.....	27	3	11.1
Transverse colon.....	4	1	25.0
Left colon.....	45	4	8.8
Totals.....	76	8	10.5

Four patients died from peritonitis; one, a woman, age 48, had severe anemia, a blood pressure of 210/114, and a considerable loss of weight before operation. She died on the twelfth day after a Hartmann procedure, as the result of wound infection, peritonitis, paralytic ileus, and hypertensive heart disease. Autopsy was not permitted. This patient might have been saved by the performance of a cecostomy or colostomy two weeks or so before the resection.

A man, age 65, died of peritonitis on the fourth day after a Rankin obstructive resection. This patient had had a cecostomy two weeks before resection. At operation, it was demonstrated that the tumor of the splenic flexure had perforated into the lateral abdominal wall, forming an abscess. There were metastases to the liver. Autopsy was secured in this case.

Another man, age 48, died on the fifth day after a resection and end-to-end anastomosis which was performed ten days after a cecostomy. The lesion was adherent to the bladder and the repair of the wound in the bladder broke down. Apparently this was the source of the infection as, at autopsy, the anastomosis proved to be intact.

The fourth patient to die of peritonitis succumbed four days after resection and end-to-end anastomosis of the transverse colon, which was followed immediately by a tube cecostomy. Metastases to the omentum were present. In this case the anastomosis broke down, as proved by autopsy. This patient, too, might well have survived surgery if a cecostomy had been established well in advance of the resection.

In the group of five surgical deaths, then, two patients might not have died had the proper preparation and treatment been instituted before resection was performed. In the last three cases, the lesions might fairly be classed as inoperable. Nevertheless, in our opinion, resection was justified, even though cure could not be expected. If such patients survive surgery, their chances for comfort during the remainder of their lives are so much improved that resection, even without hope of cure, is reasonable.

Adenocarcinoma was found in all 49 cases; 29 lesions occurred in the sigmoid colon, ten in the splenic flexure, six in the descending colon and four in the transverse colon.

Of the 49 patients, 33 are now living and well, three are living but have metastases, and 13 have died (five following surgery and eight after varying



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periods of time, Table II). These eight patients had no gross or microscopic evidence of metastasis at the time of surgery, yet they died of metastases in from six months to four years; three others are still living, but have metastases. Of these 11 patients, seven had resection with end-to-end anastomosis; two had the Mikulicz operation; one had Hartmann's resection; and one, Rankin's obstructive resection. This result is discouraging and raises the question whether the resections have been sufficiently extensive to remove all the lymphatic-bearing area. In our opinion, there is a tendency to remove too little rather than too much especially when an immediate anastomosis is planned.

TABLE II

RÉSUMÉ OF PROGNOSIS OF CARCINOMATA OF THE LEFT HALF OF THE COLON—49 CASES

	Opera- tive	Less than 1 yr.	1-2 yrs.	2-3 yrs.	3-4 yrs.	4-5 yrs.	5-6 yrs.	6-7 yrs.	7-8 yrs.	No. of Cases
Living and well.....		6	6	7	2	5	4	2	1	33
Living, with metastases				1	1		1			3
Dead.....	5	3	2	2	1					13
Total.....										49

For the future, our plan is to perform a much more extensive resection of the bowel and the mesentery in patients who show no gross evidence of metastases at the time of surgery. We know that the spread is upward and toward the midline. By performing the more extensive removal we may be unable to effect an anastomosis at the time of resection, but in some instances the bowel can be reunited at later operation. At least we shall hope to cure more of these patients.

## SUMMARY

A study of 49 cases of carcinoma of the left half of the colon is reported. The deaths in this series are analyzed and suggestions are made as to how they might have been prevented. Our method of caring for patients with disease of the left half of the colon is outlined.

## REFERENCES

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- <sup>2</sup> Hoag, Carl L.: A New Approach to Resection of Cancer of the Colonic Flexures. California and West. Med., 45, 148, August, 1936.

DISCUSSION.—DR. JOHN A. WOLFER (Chicago, Ill.): I am very happy to hear this report, and there are two or three points that I would like to stress. First is the preoperative preparation. I think that very frequently—too frequently—we push these patients suffering from carcinoma of the colon into a very serious, difficult, and long operative procedure without adequate preparation. We have been using over a period of years rather meticulous care, first, in the type of diet in attempting to reduce the putrefying organisms in the colon, giving a high carbohydrate and basal protein diet, and secondly, resorting to copious flushing of the colon in those cases that are not com-

pletely obstructed and can be cleansed. Such a regimen may require as much as six to 12 days, which I think is time extremely well spent, as has already been brought out.

The second is a procedure that I have employed during the past two or three years: After the bowel has been sectioned, for instance, in doing an end-to-end anastomosis of the left colon, we thoroughly cleanse the cups of the sectioned ends with water or salt solution followed with 5 per cent carbolic acid and 50 per cent alcohol. This seems like empiric treatment, but it came about in this way: In discussing the matter of the high mortality in colon resection with Doctor Ivy, he stated that in all his colon work upon dogs he had a tremendous mortality from infection until he began using a procedure of this type. He uses 5 per cent carbolic acid and 80 per cent alcohol, touching the edge of the cut bowel wall with 95 per cent carbolic acid. That seemed a little too drastic to me, so I compromised by using weaker solution of alcohol and omitting the 95 per cent carbolic acid.

Whether this procedure is as beneficial as I think it is, remains to be proven. However, in one instance in which we performed a resection of the sigmoid with a primary end-to-end anastomosis, with a tube decompression, I had the opportunity of seeing the abdominal cavity about one year later because of some complication that had arisen. I was unable to find the site of the anastomosis which had been performed previously, even though I could judge very well its location from the site of fixation of the colon to the abdominal wall due to the tube implantation. The lumen of the bowel was not narrowed, there was no evidence of any cicatrization, no adhesions were present, and the intestine looked perfectly normal. I am reporting this for what it may be worth. I am employing the procedure in every case of large bowel resection, and have no reason to feel other than that it is of great advantage in preventing infection of the bowel wall and contamination of the peritoneal cavity.

I am also pleased to hear the authors speak of the care in limiting the number of sutures in performing the anastomosis. I agree, thoroughly, that we destroy more lives by using a large number of sutures than we save, since each time a suture is placed through the intestinal wall a slab culture is made by carrying infectious material into the wall. Then, by tying the suture ischemic necrosis is produced. The inoculation, in the presence of devitalization, provides the essentials for infection and further necrosis. If too many sutures are placed, need we wonder why leakage takes place at the site of the suture?

We are employing one other precaution, which I believe is worth while, namely, that immediately after an intestinal resection, a gastric tube is inserted and aspiration begun at once after the operation. Wangenstein has shown that the largest amount of air or gas in the intestine consists of air that has been swallowed, and it seems logical that if the swallowed air is constantly aspirated, the intestines, in the majority of cases, can be kept perfectly deflated. This we have demonstrated to ourselves on numerous occasions.

Another point is on some work that we have recently introduced on vitamin C deficiency in surgical patients. We have found that many of the cases of malignancy have a high grade vitamin C deficiency—many in the scurvy level. Formerly, we made blood vitamin C determinations in all cases but because of the almost uniform vitamin C depletion found, all patients are now given 1,000 mg. of ascorbic acid intravenously preoperatively for a number of days, and then postoperatively during the first week or ten days until the wounds are well healed. We believe that this is another factor that will make the operative procedure safer and no doubt facilitate wound healing.

## IRRADIATION BURN OF THE INTESTINE\*

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AT THE PRESENT TIME, the accepted method of treatment of carcinoma of the cervix uteri is with interstitial radium and surface applications in the vagina, followed by high voltage roentgenotherapy to the pelvis. As a result of this technic, certain complications have been observed. In the present communication we will confine our attention to injury to the large and small intestines by irradiation. It is the impression of many that this complication is on the increase, and, furthermore, that this increase has been due to the heavier doses of radium and roentgenotherapy that have been administered in recent years. When inquiry into the relative rôle of radium and roentgenotherapy is started, one immediately encounters contrary opinions, but the author feels that the weight of evidence is in favor of radium being the chief factor. It is not, however, the purpose of this paper to further discuss this problem of the gynecologist and the roentgenologist. Rather, we plan to deal with the complication as a definite fact and shall attempt to discuss its diagnosis and treatment from the general surgeon's point of view.

Mild proctitis after treatment of the carcinoma of the cervix is not infrequent. The patient may have diarrhea, tenesmus and abdominal cramps. Proctoscopic examination will reveal hyperemia of the mucous membrane, especially at the level of the cervix. With the passage of the instrument, it is not unusual to have a little bleeding. By palpation, the mucous membrane feels soft. With palliative treatment this condition usually clears up and leaves a normal appearing mucous membrane.

Beyond this comparatively mild reaction of the mucous membrane, more severe injury to the tissue may be seen, in which the clinical symptoms become more severe, with the additional symptoms of blood and mucus in the stools. Proctoscopic examination will then reveal severe congestion of the mucous membrane with patches of ulceration. These ulcers, at first, will present soft edges to palpation, and, to vision, will show a dirty gray slough on the surface. The ulcers bleed easily on examination. Todd<sup>1</sup> has reported further changes in these ulcerated areas in which the edges have become so hard to digital examination, and resembled carcinoma so much, that she has referred to them as "pseudocarcinoma of the rectum." She reports several that were thought to be carcinoma of the rectum until biopsy had proved them to be otherwise. Todd also reports another type of extrinsic injury to the perirectal tissues, with secondary involvement of the rectum. In this second

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group, the pelvis may feel frozen, as if there had been a massive invasion of carcinoma. She reports that "the histology of both types of lesions have a striking feature in common, namely, vascular occlusion throughout, and it suggested that this phenomenon may be the vital one concerned—irradiation causing thrombosis in some of the smaller branches of the hemorrhoidal vessels, and this, spreading, leads to obliteration of the blood supply of the rectum in the junctional region, followed by the occurrence of infarction and mucosal ulceration."

Some of these cases ulcerate into the vagina to cause rectovaginal fistulae or into the perirectal tissue to cause perirectal abscesses that require incision and drainage. With palliative treatment, most of the patients with ulcer and rectovaginal fistulae will clear up and leave a smooth mucous membrane. But some will have a submucous scar formation that will constrict the lumen of the rectum—enough to interfere somewhat with stools but not enough to obstruct.

In the severe cases, colostomy may be indicated to give relief from pain and to reduce the infection in the rectum by diversion of the fecal current.

#### CASE REPORTS

**Case 1.**—Woman's Hospital No. 64177: Carcinoma of cervix. J. D., age 32, female, was treated with radium, May 8, 1937, followed by high voltage roentgenotherapy. Re-admitted, April 11, 1939, with history of intermittent lower abdominal cramps (severe enough to force her to go to bed) and obstipation, suggesting partial ileus. Barium enema showed an area of narrowing, 4 cm. long, at the rectosigmoid junction. The narrowing was smooth and the appearance was strongly suggestive of a localized radium proctitis.

**Operation** (W. C. W.)—April 15, 1939: Many peritoneal adhesions were found. The lower four inches of the sigmoid colon and part of the rectum just below the peritoneum were thickened and indurated. The peritoneal surface of the sigmoid showed white areas with punctuate red spots scattered throughout. There was no suggestion of metastases. A Mikulicz colostomy was performed, and the patient allowed to go home. She returned to the hospital in March, 1940, for closure of the colostomy. Sigmoidoscopy of the rectum through the anus, and of the sigmoid through the colostomy, revealed healthy looking mucous membrane, but some tubular contracture of the bowel. The sigmoid just admitted a seven-eighths-inch sigmoidoscope. The colostomy was closed, April 1, 1940. She was discharged, April 17, 1940, with a well-healed abdominal wound, and has been having normal bowel movements since.

It is easy to believe that radium may be the causative agent in injuries to the rectum, while the same may be said of the injury to the intestine that becomes adherent to the cervical stump.

**Case 2.**—Roosevelt Hospital No. 352464<sup>2</sup>: S., age 69, female, had had a supravaginal hysterectomy 35 years before she developed a carcinoma of the cervical stump. For this she was treated with radium and high voltage roentgenotherapy. After this she had proctitis for a short time. Six months later, she began to have lower abdominal cramps, and, one month after this, came in with acute ileus. Plain films disclosed distention of the small intestine with fluid levels in various dilated loops.

**Operation** (W. C. W.)—It was discovered that the ileum was adherent to the peritoneum over the cervical stump. When brought into the wound, the ileum was

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found to have a marked cicatricial contracture with induration, about a foot from the ileocecal valve. The ileum was resected, and a lateral anastomosis established. The specimen of the resected ileum showed an ulcer of the mucous membrane, 1x1.5 cm., with complete contracture and obstruction at this point. Microscopic study revealed no evidence of malignancy but well-defined irradiation necrosis of the ileum. (The patient died three days later, after she had developed mesenteric thrombosis that extended 200 cm. up the ileum from the site of the anastomosis.)

This case illustrates the grave risk involved in treating, with radium, a cervical stump without knowledge of the presence or absence of intestinal adhesions to the peritoneal side of the stump. It is suggested that one method of study that might be employed to see if the intestine is free, would be to have an intestinal barium series with a radiopaque substance in the vagina, in order to demonstrate the relationship. In certain cases, an exploratory celiotomy, to guard against this hazard, might be justified.

We now come to another group in which there is more reason to believe that high voltage roentgenotherapy may play a part in the damage that has been initiated by the radium. We refer to irradiation burn of the sigmoid, of which the author has had three instances. In our cases, the symptoms have come on six to eight months after treatment. T. E. Jones<sup>3</sup> has reported one such case as late as eight years after therapy. The history of these patients was similar, in that they all had diarrhea, cramps, bloody stools, and lower abdominal tenderness. All had evidence of incomplete ileus at first, and one went on to complete obstruction. A short review of each case will give best the pathology and problems to be met.

**Case 3.**—Woman's Hospital No. 65373: Carcinoma of cervix. J. L., age 35, female, was admitted, October 17, 1937, for radium only. For a short time after this treatment she had moderate proctitis. She was readmitted, July 15, 1938, with a complaint of lower abdominal cramps, bloody stools, nausea and vomiting. Barium enema showed a smooth narrowing, about one inch in length, of the proximal sigmoid.

*Operation* (W. C. W.)—A large mass was found in the upper portion of the sigmoid colon. It felt like a rubber tube. The serosa had pearly-white patches with dotted areas of telangiectasis. Ten centimeters of bowel was resected by the Gibson-Balfour technic.

*Pathologic Examination.*—*Gross:* The opened specimen revealed an ulceration of the mucous membrane, 2.5 cm. in diameter. The wall of the bowel in the region of the ulcer was transformed into scar tissue extending slightly beyond the necrosis of the mucous membrane. In April, 1940, the patient was in excellent health.

**Case 4.**—Woman's Hospital No. 68865: Carcinoma of the cervix. H. W., age 51, female, was admitted, March 6, 1939. Treated with radium and high voltage roentgenotherapy. She was readmitted, September 23, 1939, with a diagnosis of intestinal obstruction. Three weeks before admission she began to have lower abdominal cramps, diarrhea, and bloody stools. For this she had been taking barium by mouth. This had apparently not been passed, but had accumulated, dried, and initiated a complete obstruction. A cecostomy was performed by Dr. A. J. Murphy. Later, a sigmoidoscopy revealed, 13 cm. from the anus, a moderate constriction of the rectum with edema of the mucous membrane. Through this constricted ring one could see ulcers in the rectum above.

*Exploratory Celiotomy* (W. C. W.)—October 16, 1939: The uterus was fixed by a low-grade inflammatory reaction. Attached to its posterior surface, as well as to both broad ligaments, was the sigmoid colon. On separating the sigmoid from the posterior



uterus, a necrotic area was entered which contained free pus. The colon had the typical appearance of irradiation burn with patches of pearly-white serosa, and telangiectases. The sigmoid had the feel of a rubber tube. As the process involved the rectum also, it was decided to establish a colostomy in the healthy upper sigmoid. The patient did fairly well after the operation, but died of a secondary hemorrhage of the lower bowl, 34 days postoperative.

**Case 5.**—Woman's Hospital. No. 66805: Cancer of cervix, Grade II. M. A. G., age 37, female. Treatment was instituted, May 11, 1938, when radium and high voltage roentgenotherapy were administered. She was readmitted, October 16, 1938, complaining of diarrhea of several weeks' duration and lower abdominal cramps. Barium enema showed a smooth narrowing of the distal sigmoid, involving about two inches of the bowel, with a maximum caliber in this area of about one-half inch. Above and below this narrowing the bowel showed normal contour.

**Operation** (W. C. W.).—October 17, 1938: The sigmoid was found free in the abdominal cavity. It was greatly thickened and slightly kinked at one point. For a length of four inches, the serosa had a pearly-white color with telangiectatic spots scattered throughout. The thickened area was six inches in length. There was marked edema of the mesentery. There was no obvious point of necrosis in the wall. A resection of the involved area was performed, and the Gibson-Balfour anastomosis established.

**Pathologic Examination.**—*Gross:* The opened specimen revealed an ulceration of the mucosa with tissue destruction which seemed to penetrate beyond the muscular layer in areas. The muscularis was thickened to 1.2 cm. The serosa also was thickened. *Microscopic:* Necrosis and acute inflammatory reaction were demonstrated about the ulcer. The capillaries showed distention and congestion.

The patient, in April, 1940, was in excellent general condition, with the exception of a minute fecal fistula of the abdomen which apparently refused to heal. This may be due to some irradiated bowel that has deficient reparative power.

From a consideration of these cases and further thought on the nature of the pathology of this disease, the author is inclined to believe that the procedure to be employed must vary according to conditions encountered. This is influenced by the extent of the necrotizing process, with the possibility of perforation of the intestinal wall and consequent peritonitis. In one of the above cases, perforation had occurred, and in such a problem the author believes that a colostomy of either the transverse colon or the upper sigmoid colon is indicated, together with drainage of the abscess cavity. If the patient survives the operation, there is excellent prospect that the mucous membrane will gradually heal, since it is freed from the infective fecal current. Undoubtedly, there will be some contracture of the lumen of the bowel. If this is sufficient to cause obstructive symptoms, resection of that part of the bowel may be necessary. The caliber of the lumen and the condition of the mucous membrane can be determined by sigmoidoscopic examination through the colostomy wound if it is in the upper sigmoid. Barium study for evidence of obstruction and the size of the lumen may be attempted.

When the irradiation burn involves the rectosigmoid, the operation of choice is a Mikulicz colostomy with a well-formed spur. The process may subside sufficiently to permit later closure of the colostomy.

If the irradiation burn is localized in the free portion of the sigmoid that is well covered with peritoneum, a resection, with end-to-end anastomosis, is the operation of choice. Because of irradiation occlusion of blood vessels it

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is very important to go sufficiently wide of the lesion to assure good blood supply.

In addition to the ileum that was attached to the cervical stump when it received the radium burn, we have had two cases at the Roosevelt Hospital in which there was irradiation burn of ileum that must have been some distance from the cervix. T. E. Jones<sup>3</sup> has reported two such cases.

**Case 6.**—Roosevelt Hospital. No. 383053: Epidermoid carcinoma of cervix, Grade II. T. S., age 35, female, was admitted, July 26, 1938, and treated with radium and high voltage roentgenotherapy. On January 30, 1939, the patient returned with a history of intermittent attacks of lower abdominal colic followed by nausea and vomiting of 48 hours' duration. Gastro-intestinal series revealed "a narrow area of the ileum, eight inches from the cecum, with partial obstruction both to the regurgitated enema and to the barium meal. The appearance suggested organic bowel lesion from irradiation."

*Operation* (Dr. W. E. Alsop—W. C. W. present).—Fourteen inches from the ileocecal valve, a signet-ring contracture of the ileum, about three-quarters of an inch wide, was found. The bowel at this point was ischemic, and the wall of the intestine thickened. Some three inches distal to this, there was a pale disk-shaped area, three-quarters of an inch wide. There were at least four such ischemic areas in the mesentery of the ileum; also, some areas were seen on the sigmoid. The distal 24 inches of the ileum was somewhat thickened and edematous. Seven inches of ileum was resected, and a lateral anastomosis established. In April, 1940, the patient was in good health.

**Case 7.**—Roosevelt Hospital. No. 384363: B. W., age 53, female, was admitted, October 29, 1938. The patient had been treated for carcinoma of the cervix with radium and roentgenotherapy, nine months before, in California. Her complaints were nausea, vomiting, and abdominal pain. Gastro-intestinal series disclosed an ulcer of the duodenum and a narrowed terminal ileum proximal to the ileocecal valve. She was allowed to go home, and was readmitted in December, 1938, with the history that she had had constant epigastric pain, not related to food. For one week before admission, she had vomited frequently. Another gastro-intestinal study revealed an obstructive process of the small intestine, which was difficult to localize.

*Operation* (Dr. F. H. Amendola).—The head of the cecum and the terminal ileum were firmly adherent to the right pelvic brim. In dissecting this mass away, so that it could be delivered into the wound, a small abscess was encountered, which communicated directly with a large defect in the ileocecal ring, one inch in diameter. The ileocecal ring was almost stenosed as a result of fibrous contracture. The terminal ileum and proximal third of colon were resected, and a lateral anastomosis established. Pathologic examination showed chronic inflammation of ileum with ulceration of the mucous membrane. The patient died, 16 days later, of peritonitis.

### CONCLUSIONS

Irradiation burn of the intestine is a definite complication of irradiation treatment of carcinoma of the cervix. The damage to the intestine appears to be related to the amount and method of dosage as well as to the susceptibility of the patient.

The gross and microscopic pathology has been described in the course of the article. From the clinical viewpoint, it is to be noted that our cases have shown destructive action of all the coats of the intestine, although the mucous membrane, it is true, appears to be the most sensitive. When ulceration occurs in the rectal mucous membrane, it may eventually erode through

the entire wall to cause perianal abscess or rectovaginal fistula, or peritonitis when the intestine is within the abdominal cavity. If no perforation occurs, the ulcer may gradually heal up and leave an intact mucous membrane. Usually, the thickening due to fibrosis in the muscularis persists so as to reduce the caliber of the bowel. This process may go on to complete obstruction. It is interesting to note that in all our obstructive cases ulcers of the mucous membrane were present.

In mild injury to the rectum and sigmoid, palliative treatment is indicated; in the more severe cases, colostomy should be employed, in order to permit diversion of the fecal current so that the infected ulcers may have more chance to heal. Later, if this treatment is successful, the colostomy may be closed.

In localized injury to the sigmoid or ileum, resection is the method of choice.

It is the author's opinion that the injury to the sigmoid and ileum is more common than the records would indicate. The author strongly suspects that, occasionally, the opportunity to help a patient has been missed because the symptoms have been interpreted as those of a hopeless intra-abdominal recurrence. Gynecologists and general surgeons should be alert to this possibility, for success in treatment depends on early diagnosis and timely intervention, with procedures such as colostomy or resection.

Appreciations and thanks are expressed to Dr. W. E. Alsop and Dr. F. H. Amendola for permission to report their cases at the Roosevelt Hospital; also to Dr. A. H. Aldridge, Director of the Woman's Hospital, for his kindness and cooperation in the care of their cases.

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## EXPERIENCES IN CLEFT PALATE SURGERY\*

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IN 1934, we<sup>6</sup> published a paper on this subject, referring especially to the technical methods of Veau<sup>8</sup> and Dorrance.<sup>5</sup> Since that time, in our opinion, further advances have been made in these procedures, which have led to some modification of our operative methods. The principal work which has had this modifying influence is that of Axhausen,<sup>1, 7</sup> who recognizes the validity of the objections to the classic Langenbeck operation that have been advanced particularly by Veau. According to Veau the essentials for satisfactory results in cleft palate operations are: (1) An epithelial covering on the nasal side, as well as on the palatal side of the flaps; (2) obliteration of the dead space above the palatal flaps; and (3) suture of the separated palatal muscles. Axhausen has so modified the Langenbeck technic as to satisfy these requirements to a considerable degree. The technic of the operation, in the early stages, does not differ materially from that of the typical Langenbeck operation. A lateral incision is made on each side of the hard palate close to the teeth, from the tuberosity forward, and the mucoperiosteum is separated from the bone almost to the margin of the cleft. The hamular process is exposed in the lateral incision and separated with a chisel to allow the tendon of the tensor palati to be carried toward the median line, thus relaxing the soft palate. At this point, Axhausen isolates, ties and severs the palatine artery near its emergence from the foramen. The succeeding steps diverge materially from the classic operation. At the cleft margin the nasal mucosa is carefully separated from the bone to form a free flap of this tissue on each side. At the posterior edge of the hard palate, instead of cutting the nasal mucosa right through together with the aponeurosis, the continuity of this mucosa over to the soft palate is preserved, but the bony edge is carefully freed of soft tissue submucously. The free edges of the soft palate are not pared but are split to form broad raw surfaces (Fig. 1). It then becomes possible to suture the nasal mucosa across the cleft in a continuous layer from the tip of the uvula to the anterior margin of the cleft (Fig. 2). The muscles of the soft palate are then united in the median line with several catgut sutures (Fig. 3). Finally, the oral mucosa from back to front is sutured as a separate layer (Fig. 4). Packing is placed in the posterior part of each lateral incision, and Axhausen then covers the field of operation with a previously prepared celluloid plate fitting over the teeth, to hold the flaps up against the bone. We do not consider this support at all necessary, since the desired purpose is accomplished by the soft tissue sutures. Figures 5 and 6 illustrate, diagrammatically, the difference in result of the classic Langenbeck operation

\* Presented by title before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

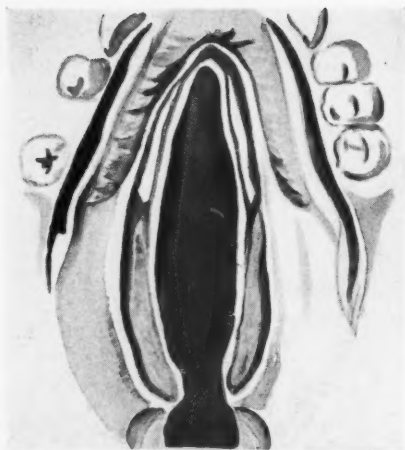


FIG. 1.—Bony edges of hard palate cleft freed of mucoperiosteum on nasal and oral sides. Posterior border of hard palate also freed of soft tissues submucously. Edges of soft palate split. (After Axhausen.)

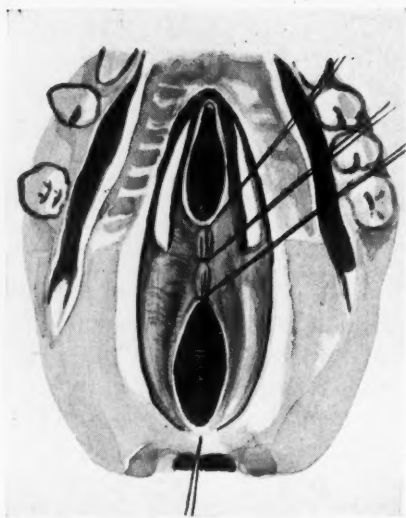


FIG. 2.—Sutures being placed in layer of nasal mucosa. (After Axhausen.)

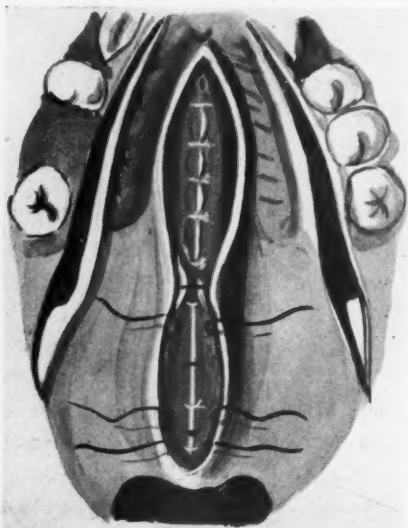


FIG. 3.—Sutures placed in muscular layer of soft palate. (After Axhausen.)

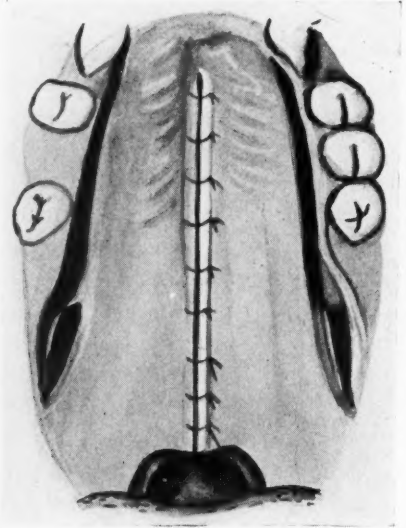


FIG. 4.—Layer of oral mucosa sutured. (After Axhausen.)

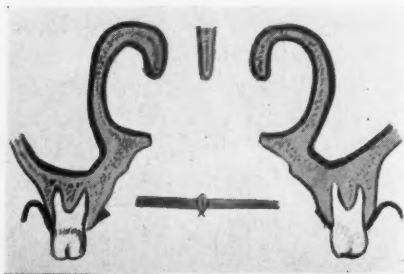


FIG. 5.—Diagrammatic cross-section showing palatal flaps sutured in classic Langenbeck operation. These flaps are not epithelialized above, and there is a dead space between them and the bone. (After Axhausen.)

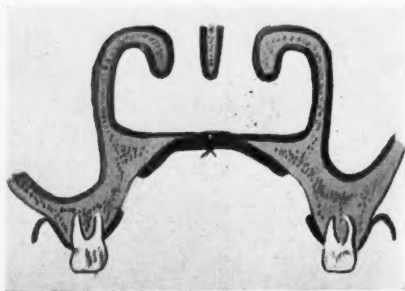


FIG. 6.—Diagrammatic cross-section showing flaps after suture in separate layers by Axhausen technic. Nasal mucosa is intact above and flaps are in close contact with bone so that dead space is minimized. (After Axhausen.)



and that of Axhausen. In the former, the nasal surfaces of the flaps are not epithelialized and there is a dead space between the bone and the upper surfaces of the flaps. In the latter, epithelium covers both oral and nasal surfaces of the flaps and the dead space is obliterated. This results in better healing with less scar tissue and less retraction and shortening of the soft palate.

During the past three years, we have employed this technic in the closure of all posterior clefts of the palate, with the exception of those falling in the class of velopharyngeal insufficiency. In clefts originally extending completely through the anterior part of the hard palate and alveolar process to the lip, either unilateral or bilateral, we still continue to deal with this anterior portion by the Veau turnover flap of mucosa from the vomer, later using the Axhausen technic for the posterior closure.

In classifying cases of cleft palate from the standpoint of operating, we find it convenient to divide them into three groups: (1) Unilateral cleft of hard and soft palate, usually associated with unilateral cleft lip; (2) bilateral cleft of hard and soft palate, usually associated with bilateral cleft lip; (3) median cleft of soft palate usually extending a varying distance into the hard palate. These are the types most commonly found, but combinations and modifications occur occasionally.

We shall now consider these different types and take up the procedures which we have found to be most satisfactory in the treatment of each type.

(1) *Complete Unilateral Cleft of Hard and Soft Palate, Associated with Unilateral Cleft Lip.*—Here, the cleft begins at the uvula, in the median line, extends forward through the soft palate, then passes on one side of the septum of the nose, the mucosa covering the vomer being continuous with the hard palate mucosa on the side opposite to the cleft. When the cleft reaches the alveolar process in front, it passes to one side of the premaxilla, and involves the lip on that side, the cleft in the lip usually passing completely through the floor of the nostril. The cleft may vary very greatly in width, and there is also a varying amount of distortion of the premaxilla, the side of this bone next to the cleft usually projecting forward. This distortion of the premaxilla has led surgeons to perform surgical reduction by cutting the bone through its attached side and fastening it back across the alveolar cleft with a wire suture. This in our opinion is entirely unnecessary, and is frequently harmful, causing undue flattening of the bone and upper lip and injury to tooth germs. This bone will usually assume correct position in time by pressure of the closed lip if the lip cleft be closed at an early age.

In this type of case, we advocate the following procedures: At from six weeks to three months of age, we combine the first-stage Veau operation on the hard palate and alveolar cleft with closure of cleft in the lip. The Veau procedure should be performed before the lip is closed, since this will nearly always insure complete closure of the cleft in the alveolar process all the way

to the front under the lip. If the lip is closed first, it is quite difficult to obtain this complete closure in front beneath the lip. The Veau technic has been frequently described,<sup>8</sup> but a brief résumé may not be out of place: Use is made of a flap of mucoperiosteum from the vomer, this flap being turned over so that its epithelial surface faces upward to form the lining of the floor of the nose on the side of the cleft, from near the posterior end of the hard palate to the cleft of the lip anteriorly (Fig. 7). On the short side of the cleft, a palatal mucoperiosteal flap is completely detached at its anterior end, raised from the bone from before backward, and swung across the cleft, with

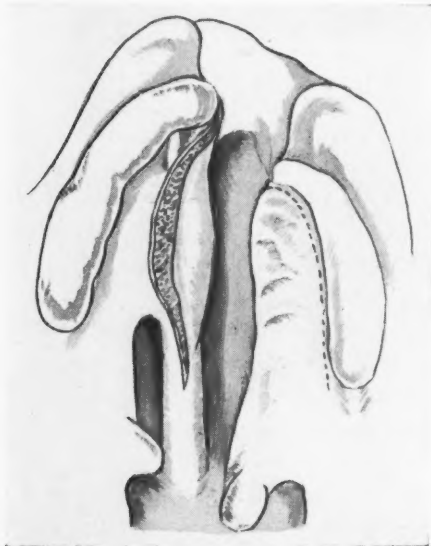


FIG. 7.—Flap of mucoperiosteum from vomer being raised. Mucoperiosteal flap from outer side of hard palate outlined. (After Veau.)

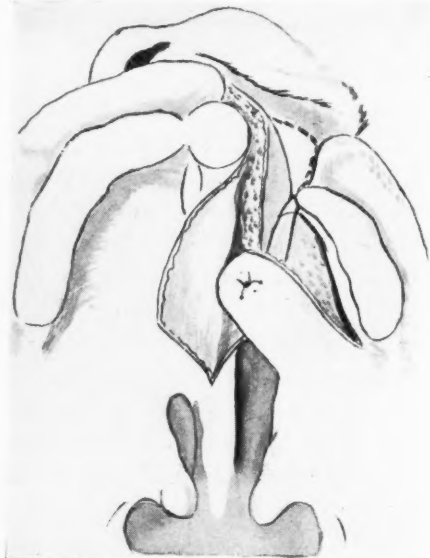


FIG. 8.—Flap from vomer turned over to form floor of nose and palatal flap from opposite side of cleft swung over and sutured to it. (After Veau.)

its raw surface applied to the raw surface of the vomer flap (Fig. 8). These two flaps are held together with one or two through-and-through silk sutures. The nasal mucosa on the short side of the cleft is loosened from the bone for a distance and turned over, so that it can be sutured to the anterior end of the vomer flap, thus closing the cleft under the lip (Fig. 9). The operation is now completed by closure of the lip cleft by the Blair-Mirault<sup>2</sup> technic. This raising and shifting of flaps creates considerable raw surface in the hard palate, but this rapidly heals over, leaving only a cleft in the soft palate and posterior part of the hard palate, to be closed not before two and one-half to three years of age by the Axhausen method, already described.

(2) *Complete Bilateral Cleft of Hard and Soft Palate, Associated with Bilateral Cleft Lip.*—Here, the cleft extends in the midline through the uvula, soft palate and hard palate, with the lower border of the septum of the nose lying free in the cleft, so that there is a communication with both sides of the nose. On each side of the premaxilla the cleft extends through the alveolar

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process and lip. The anterior end of the vomer bearing the premaxilla is frequently elongated, carrying the premaxilla and philtrum of the lip abnormally far in advance of the lateral portions of the maxilla and lip. Here also, there is a temptation to cut the advanced premaxilla loose from the vomer and carry it back between the lateral walls of the cleft and facilitate closure of the lip. This procedure frequently results in undue flatness of the upper lip, atrophy of the premaxilla, permanent nonunion, and backward position of the upper anterior teeth when they erupt. It is much better not to disturb the protruded premaxilla at this time, but to close the lip cleft over it, and

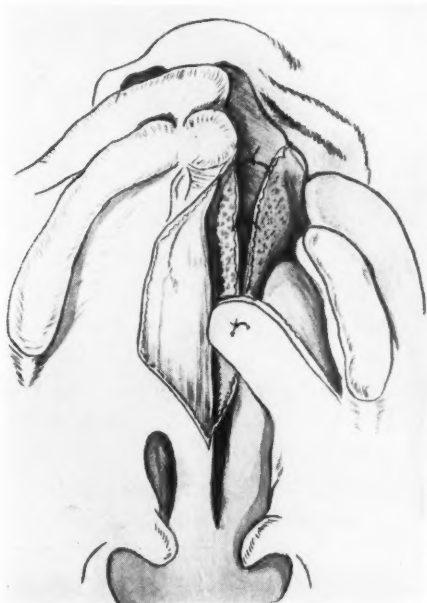


FIG. 9.—Nasal mucosa freed anteriorly and sutured to front of vomer flap to close cleft under lip. (After Veau.)

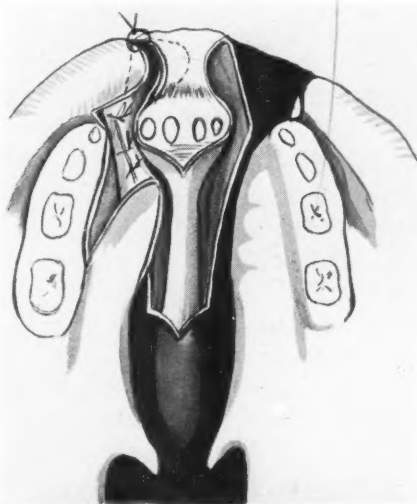


FIG. 10.—Closure of anterior part of bilateral cleft on one side by vomeropalatal flap technic, converting bilateral into unilateral cleft. The other side is closed a few weeks later. (After Veau.)

if this does not suffice to gradually bring it into correct position, a later operation can be done for this purpose. In these bilateral cases the same principle is followed as for the unilateral cases, except that one side is operated on at a time, the bilateral cleft being first converted into a unilateral one. The vomer mucosa is split longitudinally and a flap turned over on one side, to be sutured beneath a mucoperiosteal flap raised on one side of the hard palate. The corresponding side of the lip is closed at the same sitting (Fig. 10). A few weeks later the opposite side of the cleft is closed in a similar manner. The case is completed by closure of the posterior part of the cleft by the Axhausen technic at two and one-half to three years of age.

(3) *Median Cleft of Soft Palate Usually Extending a Varying Distance into the Hard Palate.*—Cases of this group may vary from a split in the uvula and soft palate alone, to involvement of the hard palate right up to the pre-

maxilla. These clefts are always in the midline and the lower edge of the vomer may be free. They vary very greatly not only in length but also in width, and may present great difficulty in successful closure. Velopharyngeal insufficiency is more common in this type of cleft than in the other types. Many operators advocate closure of these clefts at an early age, varying from six to 18 months, on the plea that speech will be better if the cleft is closed before the child begins to talk. We do not believe that the chances for good speech results are materially impaired by waiting until two and one-half to four years of age before closure of the posterior cleft. At the later age the mortality will be lower and the chances of good anatomic closure much better. During the past three years we have employed the Axhausen technic, already described, for closure of this type of cleft.

A summary of the age at time of operation and the procedure employed is shown below:

APPROXIMATE AGE AND PROCEDURE RECOMMENDED FOR TREATMENT OF  
VARIOUS FORMS OF CLEFT LIP AND PALATE

(1) *Complete Unilateral Cleft of Hard and Soft Palate:*

(a) Six weeks to three months—Veau turnover flap from vomer to close anterior part of hard palate, followed at same sitting by closure of lip cleft by Blair-Mirault procedure.

(b) Two and one-half to three years—Axhausen operation for remaining cleft in hard and soft palate.

(2) *Complete Bilateral Cleft of Hard and Soft Palate:*

(a) Six weeks to three months—Veau turnover flap from vomer to close anterior part of hard palate on one side, followed at same sitting by closure of lip on same side by Blair-Mirault procedure, converting bilateral into unilateral cleft. Followed, about four weeks later, by same procedure on opposite side. In most cases the protruding premaxilla gradually assumes correct position by pressure of closed lip.

(b) Two and one-half to three years—Axhausen operation for closure of remaining cleft in hard and soft palate.

(3) *Median Cleft of Soft Palate Usually Extending a Varying Distance into the Hard Palate:*

Two and one-half to three years—Axhausen operation.

(4) *Cases of Velopharyngeal Insufficiency:*

For cases of cleft palate, where the usual operations would not provide sufficient tissue posteriorly to permit velopharyngeal closure, excellent speech results may be obtained by the "push-back" operation of Dorrance, usually performed in two stages, not earlier than four years of age. This operation is also recommended as a secondary procedure where other methods have given inadequate velopharyngeal closure. The modification published by Barrett Brown<sup>3, 4</sup> permits a one-stage procedure with safety.

Cases treated during the past three years, since we have employed the above-described technic, on the author's service at the Presbyterian, Graduate

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and University Hospitals, in association with Dr. Lawrence Curtis and Dr. Henry A. Miller, may be grouped as follows:

(Results are recorded as Good, in which no secondary operations were necessary; Fair, in which an opening remained, requiring secondary operation for closure; Failure, in which the operation was completely unsuccessful.)

(1) Complete Unilateral Cleft Palate, in which the Veau-Axhausen Sequence Was Followed:

Number of Cases	—Result—	
	Good	Fair
27	21	6

(2) Complete Bilateral Cleft Palate, in which the Veau-Axhausen Sequence Was Followed:

Number of Cases	—Result—	
	Good	Fair
9	8	1

(3) Median Cleft, in Which the Axhausen Operation Was Performed:

Number of Cases	—Result—	
	Good	Fair
21	12	9

(4) Cases of Velopharyngeal Insufficiency, in Which the "Push-Back" Operation Was Performed:

(a) Primary Cases

Number of Cases	—Result—		
	Good	Fair	Failure
15	11	2	2

(b) Secondary Cases

Number of Cases	—Result—	
	Good	Fair
5	4	1

Total No.  
of Finished

Cases	—Result—		
	Good	Fair	Failure
77	56	19	2

(5) Unfinished Cases, in Which Only the First-State Veau Operation has, So Far, Been Performed:

	Number of Cases	—Result—		
		Good	Fair	Failure
(a) Unilateral	18	16	1	1 (death)
(b) Bilateral	8	7	1	—
Total	26	23	2	1

In addition to these, there were 53 cases in which miscellaneous secondary operations were undertaken in order to improve results in cases primarily operated upon elsewhere.

The results so far obtained in this series of cases encourage us to continue with the procedures described above, as a routine in typical cases of cleft palate.

I am indebted to Dr. Henry A. Miller for looking up the records of the cases.

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# THE USE OF INTRAMUSCULAR INJECTIONS OF 2-METHYL-1, 4-NAPHTHOQUINONE IN THE TREATMENT OF PROTHROMBIN DEFICIENCIES\*

WITH A NOTE ON THE RÔLE OF THE LIVER IN THE RESPONSE TO THIS AND OTHER SUBSTANCES WITH VITAMIN K ACTIVITY

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THE DEMONSTRATION of a deficiency in the prothrombin activity of the plasma as the responsible factor in the hemorrhagic tendency sometimes occurring in obstructive jaundice and hemorrhagic disease of the newborn, and the experimental and clinical evidence which has accumulated during the past few years indicating the vital rôle played by the accessory food factor known as vitamin K in the production of prothrombin, have, logically, stimulated the purification and identification of the vitamin. It, apparently, occurs in at least two forms which have been identified by MacCorquodale, Binkley, Thayer and Doisy,<sup>1</sup> and by Fieser and his coworkers.<sup>2</sup> Almquist and Klose<sup>3</sup> had previously shown that phthiocol (2-methyl-3-hydroxy-1, 4-naphthoquinone) possessed vitamin K activity, and a large number of other naphthoquinones have since been investigated. Of all those tested, however, it has become evident that only the 1, 4-naphthoquinones have this property, and of these, by far the most potent is synthetic 2-methyl-1, 4-naphthoquinone. These substances have now largely supplanted the cruder extracts formerly used, and while there is some difference of opinion as to the potency of 2-methyl-1, 4-naphthoquinone as compared to the crystalline vitamin, most workers are in agreement that its effectiveness is at least equal to, or even surpasses, that of the vitamin itself. This fact, together with the ease with which it can be synthesized, makes 2-methyl-1, 4-naphthoquinone the best available agent for the correction of prothrombin deficiencies.

It has been successfully employed in a number of clinics, and can be administered orally,<sup>4, 5</sup> intramuscularly<sup>6, 7</sup> or intravenously. For intramuscular injection, the crystalline substance is dissolved in corn oil and for intravenous use, either 2-methyl-1, 4-naphthoquinone 1 mg. in 10 cc. of distilled water or a more soluble derivative may be employed. We believe the intramuscular route to be the simplest and most effective, since there is no reaction at the site of injection and the effect is evident within a few hours.

Presented by Title before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

\*This study was carried out under a grant from the John and Mary R. Markle Foundation.

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# THE USE OF INTRAMUSCULAR INJECTIONS OF 2-METHYL-1, 4-NAPHTHOQUINONE IN THE TREATMENT OF PROTHROMBIN DEFICIENCIES\*

WITH A NOTE ON THE RÔLE OF THE LIVER IN THE RESPONSE TO THIS AND OTHER SUBSTANCES WITH VITAMIN K ACTIVITY

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THE DEMONSTRATION of a deficiency in the prothrombin activity of the plasma as the responsible factor in the hemorrhagic tendency sometimes occurring in obstructive jaundice and hemorrhagic disease of the newborn, and the experimental and clinical evidence which has accumulated during the past few years indicating the vital rôle played by the accessory food factor known as vitamin K in the production of prothrombin, have, logically, stimulated the purification and identification of the vitamin. It, apparently, occurs in at least two forms which have been identified by MacCorquodale, Binkley, Thayer and Doisy,<sup>1</sup> and by Fieser and his coworkers.<sup>2</sup> Almquist and Klose<sup>3</sup> had previously shown that phthiocol (2-methyl-3-hydroxy-1, 4-naphthoquinone) possessed vitamin K activity, and a large number of other naphthoquinones have since been investigated. Of all those tested, however, it has become evident that only the 1, 4-naphthoquinones have this property, and of these, by far the most potent is synthetic 2-methyl-1, 4-naphthoquinone. These substances have now largely supplanted the cruder extracts formerly used, and while there is some difference of opinion as to the potency of 2-methyl-1, 4-naphthoquinone as compared to the crystalline vitamin, most workers are in agreement that its effectiveness is at least equal to, or even surpasses, that of the vitamin itself. This fact, together with the ease with which it can be synthesized, makes 2-methyl-1, 4-naphthoquinone the best available agent for the correction of prothrombin deficiencies.

It has been successfully employed in a number of clinics, and can be administered orally,<sup>4, 5</sup> intramuscularly<sup>6, 7</sup> or intravenously. For intramuscular injection, the crystalline substance is dissolved in corn oil and for intravenous use, either 2-methyl-1, 4-naphthoquinone 1 mg. in 10 cc. of distilled water or a more soluble derivative may be employed. We believe the intramuscular route to be the simplest and most effective, since there is no reaction at the site of injection and the effect is evident within a few hours.

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Its action is also, definitely, more prolonged than when the substance is given orally. Thus, a single injection of 2 mg. has elevated the prothrombin of patients by as much as 40 per cent, and in one individual, 11 days elapsed before it again fell. Tage-Hansen<sup>8</sup> noted similarly prolonged effects when large doses of purified vitamin K were injected intramuscularly. Further points in favor of the parenteral route are certainty of absorption and the lack of need for the coincident administration of bile salts which are not always well tolerated.

Since October 1, 1939, we have administered 2-methyl-1, 4-naphthoquinone, intramuscularly, to 49 patients with initial plasma prothrombin levels of from 5 to 80 per cent of normal by the test of Warner, Brinkhous and Smith.<sup>9</sup> Doses of 2 mg. were employed routinely—except in infants who received from 0.35 to 1 mg.—and with uniformly good results in the absence of severe liver damage. In many instances, a single injection of 2 mg. sufficed to restore the plasma prothrombin to a satisfactory level, and, in most, the higher level was maintained for from several days to a week or even longer, but in some the injection was repeated at two- or three-day intervals. Daily injections of the same, or even twice the amount for two to four days, were employed in those cases in which the presence of severe liver damage made the response less likely to be satisfactory. The types of cases in which this therapy was employed and the response in percentage of the normal level obtained to a single injection of 2-methyl-1, 4-naphthoquinone are shown in Table I.

TABLE I

Diagnosis	No. of Cases	Response in Percentage of Normal
Obstructive jaundice due to stone.....	12	4-48
Obstructive jaundice due to stricture.....	1	11
Carcinoma of head of pancreas.....	4	10-40
Catarrhal jaundice.....	2	1-6
Cirrhosis of the liver.....	5	Continued to fall
Liver abscesses with empyema.....	1	12
Liver abscesses— <i>Cl. welchii</i> .....	1	0
Cholelithiasis.....	1	33
Hemorrhagic disease of newborn.....	10	5-30
Carcinoma of stomach.....	3	10-20
Peptic ulcer.....	1	28
Faulty gastro-intestinal absorption.....	2	28-29
Repeated gastro-intestinal hemorrhage—unknown origin...	1	18
Idiopathic purpura.....	1	38
Thrombasthenia.....	1	28
Empyema, sepsis.....	1	35
Nephrosis with septicemia.....	1	47
Endocrine imbalance.....	1	12
Total.....	49	



In view of the mass of accumulated clinical evidence that liver damage interferes with the response to substances with vitamin K activity, it is important to consider the normal rôle of the liver in the metabolism of vitamin K and the production of prothrombin. The available evidence indicates that this organ, aside from the production of bile salts which are necessary in the absorption of the vitamin from the intestinal tract, is a storehouse of the vitamin itself. Thus, after its absorption, the vitamin is stored in the liver, probably in a somewhat altered form,<sup>10</sup> and this reserve is gradually depleted when, for any reason, continuous absorption from the intestinal tract is interfered with. Concomitant with the disappearance of the vitamin from the liver, the level of the plasma prothrombin falls<sup>10</sup> and the hemorrhagic tendency becomes evident when it reaches a certain critical level. Thus, an animal or patient may develop a prothrombin deficiency without liver damage after a time, when the vitamin is no longer absorbed from the intestinal tract due to absence of bile, as in obstructive jaundice or biliary fistula, or in certain cases of severe enterocolitis. When the vitamin is supplied, however, prompt restoration of the plasma prothrombin follows in these cases.

Experimental evidence also indicates that the prothrombin normally disappears from the plasma at a fairly rapid rate, so that any interference with its production will be soon followed by a drop in the plasma prothrombin level. The site of its disappearance appears to be in the lungs, as it has been shown<sup>11</sup> that there is an appreciable difference in the level of the plasma prothrombin in blood from the right and left sides of the heart.

The effect of liver damage on the plasma prothrombin level has been demonstrated experimentally by a number of workers. Thus, Smith, Warner and Brinkhous<sup>12</sup> noted a fall in the plasma prothrombin level to less than 5 per cent of normal after 90 minutes of chloroform anesthesia. Lord<sup>13</sup> found that gentle massage of the liver was followed by a depression of the prothrombin level amounting to 25 per cent, a possible contributing factor in hemorrhage in jaundiced patients after operation. Warner<sup>14</sup> showed that removal of 65 per cent of the liver in rats also caused a fall which was recovered from in about two and one-half weeks. Warren and Rhoads,<sup>15</sup> and Andrus, Lord and Moore,<sup>16</sup> independently, found that complete hepatectomy in dogs caused the plasma prothrombin to fall to below 10 per cent of normal within 14 hours, and the latter authors demonstrated that the administration of 10,000 units of vitamin K and bile salts into the intestinal tract failed to prevent this drop. We have since repeated this work, using as much as 80,000 units of 2-methyl-1, 4-naphthoquinone intramuscularly and intravenously, without affecting the curve of fall of the plasma prothrombin after hepatectomy.

The failure of patients with varying degrees of liver damage to respond adequately, or at all, to the administration of substances with vitamin K activity, has been widely noted by clinicians. Thus, Quick,<sup>17</sup> Butt, Snell and Osterberg,<sup>18</sup> and others<sup>19, 20, 21</sup> reported cases in which poor response was obtained and attributed this to liver damage. In December, 1938, we observed

a case which strikingly demonstrated the effect of liver damage on the utilization of vitamin K. The patient, female, age 50, was admitted with jaundice due to stone in the common duct and acute cholecystitis. The plasma prothrombin was only 25 per cent on admission, but rose very satisfactorily to normal during the next four days on the administration of Cerophyl and bile salts. Despite the continued administration of the vitamin, however, the patient's prothrombin then fell precipitously and remained below 30 per cent thereafter. At postmortem, the liver showed the following:

**Case 1.**—E. B. New York Hosp. No. 221902: Massive liver necrosis, secondary to thrombosis of the hepatic artery and the portal vein.

*Pathologic Examination.*—*Gross:* The liver together with the duodenum and pancreas weighs 2,350 Gm. The surface is nodular and mottled red, bluish-purple and yellow. On section, the peripheral 6 cm. is dark, cystic, mottled green, yellow and dark red. It is crepitant. There are numerous similar areas scattered throughout the inner portion, the normal architecture of which is preserved but much bile-stained. An approximate two-thirds to three-quarters of the parenchyma is necrotic. The bile ducts contain in many cases a brown, firm material. Numerous intrahepatic branches of the portal vein contain firm, brown material. There is a large organizing thrombus, approximately 5 cm. in length, in the portal vein before it branches. There is a 2 cm. firm, friable thrombus attached to the wall of the hepatic artery 4 cm. below its branching.

*Microscopic:* The cords are broken and fragmented. The cells are swollen and granular. This is especially conspicuous in the central portions of the lobule where throughout the section the sinusoids are large and filled with pink, granular material, erythrocytes and a few polymorphonuclear leukocytes. The liver cells in these areas are ill-defined, and contain much brown pigment. The biliary canaliculi are engorged with brown material. This is more advanced in some areas than others. The periportal tissue is slightly increased and infiltrated with lymphocytes. Many of the bile ducts in these spaces are distended with brown material. Clumps of granular, blue substance are scattered throughout the section, indiscriminately. There are a few hemorrhages. Throughout all the sections are large areas where the normal architecture is lost, the liver cords fragmented and the necrotic cells separated by large and small spaces, some of which contain pink, granular material. In one section is a vessel in which there is an organized thrombus.

In the earlier cases, the possibility that the vitamin might have been poorly absorbed threw some doubt on the implication of the liver in the poor response although in this case the primary response was excellent, but since the highly potent 2-methyl-1, 4-naphthoquinone has been available, and similar failures have followed its parenteral administration, the connection between liver damage and inadequate restoration of prothrombin levels after the administration of the vitamin would seem to be established.

Since our experience with the case mentioned above, we have encountered nine additional patients with lowered plasma prothrombin levels who failed to respond to even relatively large doses of substances with vitamin K activity. Eight were treated with intramuscular injections of 2-methyl-1, 4-naphthoquinone and one received Klotogen and bile salts by mouth. Three of these patients have clinical evidence of liver damage as indicated by liver function tests, and in the remaining six, it has been possible to study the liver either at operation (two cases) or at postmortem. All showed pathologic changes

of severe grade, but the types of lesions encountered were so diverse as to shed little light on the exact condition responsible for the decreased prothrombin production. The pathologic descriptions of the liver in these cases were as follows:

**Case 2.**—A. G. New York Hosp. No. 241700: Periportal cirrhosis, cholangitis.

*Pathologic Examination.*—*Gross:* The liver weighs 2,070 Gm. The surface is roughened by nodules measuring up to 2 Mm. across. The organ is dark green-brown. On section, the normal lobular architecture is replaced by a nodular architecture. These nodules are for the most part small and measure up to 3 Mm. across and are separated from one another by dense gray-white fibrillar tissue. These nodules vary in color from green to dark brown. The intrahepatic portal spaces visible show no changes. The organ is increased in consistency.

*Microscopic:* The capsule is slightly thickened and infiltrated with lymphocytes. The normal lobular architecture of the liver is distorted by fragmentation of the liver cords, by eccentricity of the central veins, and by conspicuous increase in the periportal connective tissue. The cytoplasm of the individual liver cells is granular, acidophilic, and contains brown pigment granules. The cords are fragmented and widely separated by sinusoids distended with blood and by fibrous tissue. The sinusoidal epithelium is separated from the cords of liver cells by small amounts of pink, granular material. In a small number of places through the section the bile canaliculi are distended by inspissated bile. The periportal spaces and lobules are infiltrated by large numbers of lymphocytes and polymorphonuclear leukocytes. Proliferating bile ducts in these areas are numerous. Many bile ducts have polymorphonuclear leukocytes in the lumen and in the epithelium.

**Case 3.**—J. P. D. New York Hosp. No. 256206: Cirrhosis with central necrosis.

*Pathologic Examination.*—*Gross:* The liver is slightly enlarged, weighing 2,200 Gm. It is yellow-gray in color, and moderately firm. The capsule appears thickened and the surface is finely nodular. On section, the substance appears to be made up of many small nodules of hepatic tissue up to 3 Mm. in diameter, embedded in a moderately dense fibrous stroma. No definite areas of necrosis are seen.

*Microscopic:* Thick bands of connective tissue, moderately infiltrated with round cells, separate the liver substance into irregular lobules of various sizes. In many of the fibrous regions are seen numerous small bile ducts. The hepatic cells, generally, show no changes at the periphery of lobules, but in the central portions are wide areas of recent necrosis, probably involving one-fourth of the hepatic cells in the section. In the more normal hepatic cells the canaliculi contain bile pigment.

**Case 4.**—T. H. New York Hosp. No. 256106: Pylephlebitis with multiple liver abscesses.

*Pathologic Examination.*—*Gross:* The liver weighs approximately 3,000 Gm.; it is pale, soft and friable. There is fibrinopurulent exudate over many parts of the liver and it is most conspicuous in the inferior lateral part. Above, the liver is adherent to the diaphragm. The cut-surface of the right lobe of the liver is studded with many abscesses that vary from a few millimeters up to 7 cm. across. A few of them are lined with a pyogenic membrane and are filled with a thick, creamy, odorless pus. Others are not so well circumscribed and contain bile. The largest abscesses are in the interior-posterior part of the liver. There are a few smaller abscesses in the left lobe. The portal vein is filled with an infected thrombus that extends along the splenic and superior mesenteric veins for a considerable distance. The gallbladder is of normal size, is edematous and the mucosa is injected. The bile contains a considerable amount of purulent material. The ducts are patent.

*Microscopic:* The capsule is thick and covered in one area with a necrotic fibrinous exudate. There are several circumscribed abscesses throughout the section some of which

are composed predominately of monocytes and necrotic liver tissue. These abscesses have undergone complete necrosis. There are bile thrombi in several of the bile ducts.

**Case 5.**—G. G. New York Hosp. No. 258992: Multiple liver abscesses with widespread gas bacillus infection.

*Pathologic Examination.*—*Gross:* The liver weighs approximately 250 Gm. It is intimately adherent to the stomach and the granulating wound of the anterior abdominal wall. A sinus tract in the center of the large granulating wound of the anterior abdominal wall can be probed to a depth of 9 or 10 cm. and is in communication with the interior of the liver. The external surface of the liver is brown in color and is mottled by lighter brown areas in the usual way. There is an incision 3 cm. in length on the anterior surface of the liver. This extends 1 cm. into the liver substance. A number of fine fibrinous adhesions roughen the external capsular surface. The liver is fluctuant and, on section of the right lobe, a large amount (approximately 200 cc.) of very foul, green, purulent material escapes. Cuts made in other portions of the liver reveal similar changes throughout the entire organ, replacing approximately 60 to 70 per cent of the liver substance. In the left lobe of the liver is a large area with a honeycomb-like structure. The borders are composed of light brown tissue, arranged in a circinate manner. The liver tissue, outside of these areas of frank abscess formation, is apparently well preserved and has the usual architectural pattern. Cultures of the pus yielded *Cl. welchii* and streptococci.

*Microscopic:* The first section was taken from an area of abscess formation, and is made up largely of polymorphonuclear leukocytes, necrotic liver cells and clusters of bacteria. Between the abscesses there is, however, a surprising amount of good liver tissue remaining. The portal areas are infiltrated extensively by inflammatory cells. The chief cells are lymphocytes, but there are a large number of plasma cells and polymorphonuclear leukocytes. Careful study of cross-sections of the bile ducts fails to reveal any inflammatory exudate within them. The sinusoids between the liver cords are widely dilated and contain large numbers of polymorphonuclear leukocytes as well as considerable cellular debris. The liver cells contain large quantities of bile pigment. One small vein contains a thrombus made up of polymorphonuclear leukocytes, platelets and fibrin.

The second section of liver was taken from the periphery of the organ, away from the areas of massive abscess formation. The capsule is moderately thickened and infiltrated by inflammatory cells. These are chiefly lymphocytic in type. There is dilatation of the lymphoid spaces, within and beneath the capsule. There is marked increase in fibrous tissue in some of the portal areas which are infiltrated by similar inflammatory cells. The sinusoids are dilated and infiltrated by numerous polymorphonuclear leukocytes. This is most conspicuous in the central portion of the lobules. The cells within the central portions of the lobules contain large quantities of bile pigment.

**Case 6.**—C. M. New York Hosp. No. 226577: Subacute periportal hepatitis.

Surgical pathologic report on biopsy taken at operation:

*Pathologic Examination.*—*Gross:* Specimen consists of a small wedge of dark red liver tissue, measuring 6x4x3 Mm. It is in no way grossly remarkable except that it is very firm.

*Microscopic:* There is destruction of the normal architecture of the liver by the periportal inflammation. Many liver cells have undergone fatty degeneration. Surrounding the blood vessels and bile ducts, in the periportal areas, there is evidence of hemorrhage and proliferation of fibrous tissue. Bile pigment deposits are present in these areas and an infiltration with polymorphonuclear leukocytes and monocytic cells.

**Case 7.**—P. L. New York Hosp. No. 255971: Laënnec's cirrhosis.

Description of the operative pathology of the liver: "The liver was found to be extremely small, perhaps less than half its normal size, discolored and dark brownish in color, finely nodular, and everywhere very firm, presenting the picture of a very advanced cirrhosis. The liver edge lay about 6 cm. above the costal margin."

SUMMARY

(1) Forty-nine patients with levels of plasma prothrombin activity between 5 and 80 per cent of normal, by the test of Warner, Brinkhous and Smith, have been treated by means of intramuscular injections of 2-methyl-1, 4-naphthoquinone with very satisfactory response in 41.

(2) In three of these 49 patients, there was clinical evidence of liver damage, as indicated by liver function tests, but its exact nature is not yet known. In the five others, who failed to respond to 2-methyl-1, 4-naphthoquinone, and in two additional cases, not included in the above series, who were treated with Cerophyl or Klotogen but whose prothrombin did not rise despite continued administration of the vitamin, the presence of marked liver damage was definitely proved—at operation in two cases or at postmortem examination in five cases.

(3) These seven patients presented a wide variety of pathologic pictures, including Laënnec's cirrhosis, cholangitis, periportal hepatitis, multiple liver abscesses complicating pylephlebitis, gas bacillus infection, cirrhosis with central necrosis, and massive infarction of the liver secondary to thrombosis of the hepatic artery and portal vein.

(4) These lesions were so diverse in nature and so widespread in extent as to yield little information regarding any specific type of liver injury responsible for the decreased prothrombin production.

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## FURTHER ANESTHESIA STUDIES WITH PHOTO-ELECTRIC OXYHEMOGLOBINOGRAPH\*

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THE DATA we wish to present are a continuation of studies on anoxia in surgery, presented to the Association last year. Those studies on experimental animals and surgical patients were made through the application of Warburg's method for tissue respiration and Van Slyke's manometric method for oxygen saturation of the arterial blood. Both of these methods are not only slow and laborious but, at best, can be applied only at intervals.

During the course of this earlier work the necessity for continuous observations of the oxygen saturation became apparent, and the work of Kurt Kramer and Karl Matthes, published in 1934 and 1935, was reviewed. Both investigators measured the oxygen saturation of the blood by means of light absorption as determined with photo-electric cells and galvanometers. This work was fundamental, as seen in the following excerpts from their papers. Kramer, 1934: "For the study of metabolic-physiologic problems a method was needed which would permit the easy determination of the oxygen content of the blood at short intervals or even continuously in the animal body. This requirement was not met by any of the methods thus far used, including the manometric determination of Van Slyke and the improved spectral analytic determination of Routon and Hartridge. . . . The development of the photo-electric cell technic, especially Lange's barrier layer cells, made it possible to utilize the spectral peculiarities of hemoglobin to carry out oxyhemoglobin determinations *in vitro* and, perhaps, *in vivo* quickly and accurately." Through these investigations Kramer confirmed the validity of Beer's law for hemoglobin solutions.

Based on the original observations, the second paper, of 1935, reported a method for the continuous oxygen analysis of the blood in closed vessels of an animal with accuracy to 1 per cent saturation. In explanation, Kramer stated: "It has been demonstrated that the light absorption of hemoglobin solutions even in high concentrations, is subject to Beer's laws. It, therefore, could be assumed that the condition of the hemoglobin molecule of the normal blood which is found in the erythrocyte, in 30 per cent concentration, would not greatly complicate the laws of light absorption. Therefore, the light permeability of the hemoglobin, which varies with the oxygen content, had to be fundamentally similar to the photo-electric findings in pure hemoglobin solutions. The principle of the method is based on the spectral differences of the hemoglobin and oxyhemoglobin in the red wave length section."

\* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

Karl Matthes, 1934: "Since the fluctuations of the filling of the pulmonary reservoir are changing rapidly, the analysis of blood samples obtained by puncture permitted only a very inadequate picture of the entire process. We, therefore, searched for a method for continued recording of the oxygen content of the blood in arteries and veins. Such a possibility was presented by the well-known differences in the light absorption of oxyhemoglobin and reduced hemoglobin. After the technical part of these investigations had been completed, Kramer published a method very similar in principle." Matthes used mercury vapor lamp after Nicolai. Kramer used ordinary light with Zeiss-red filter R.G.I.—"A method has been evolved which permits the continuous optical registration of the oxygen content and the total concentration of the hemoglobin in the blood of a given vessel, instead of periodic withdrawal of blood which is subject to many technical disadvantages.

"The principle of the new technic which employs photo-electric methods consists in the registration of the absorption of light of two spectral regions through the blood." Under the title "Investigation of the Oxygen Saturation of Human Arterial Blood," Matthes, in 1935, applied the red-sensitive photocell used by Kramer to the ear lobe after histamine iontophoresis. In conjunction, in order to evaluate the passive fluctuations of the vascular bed, a plethysmogram of the other histamized ear lobe was made. These simultaneous records allowed the immediate recognition and the elimination of all distortions of the oxygen saturation curve caused by changes of the blood content of the ear lobe. The oxygen saturation curve was calibrated by blood determinations during oxygen, air and 88 per cent nitrogen respiration. During the first, the saturation was found always to be 100 per cent.

From this analysis of the work of Kramer and Matthes it seems demonstrated that measurement of light absorption by red-sensitive photo-electric cells is capable of giving accurate oxygen saturation values for hemoglobin *in vitro*, in blood vessels or in selected skin areas providing other variables, especially the total hemoglobin in the circulation and the volume of the part within the cell, are taken into consideration. The first of these variables is of secondary importance since large enough changes in the total hemoglobin occur only after adrenalin to materially alter the oxygen saturation values. The second of the variables, that is volume of the part, should be recorded in parallel as it was by Matthes. Kramer dealt with large vessels, filling his rigid cells, thus avoiding this factor. Matthes histamized the ear lobe used and generally obtained plethysmographic records of the other ear lobe using a combination volume and photo-electric cell method. In 1937 and 1938, Hertzman, of St. Louis University, described the use of a photo-electric plethysmograph, for studying the blood supply of various skin areas. This apparatus resembles that of Kramer and Matthes except that a photo-electric cell of the photo-emissive type rather than the red-sensitive or the green-sensitive type was used. Hertzman mentions the influence of reduced

hemoglobin-oxygenated hemoglobin ratio on skin opacity, but his detailed observations apparently have not been published.

#### SUMMARY

(1) In our work, thus far, volume changes of the parts incorporated in the photo-electric cell have not been recorded in parallel, but with the increasing stability and dependability of the machine, volume changes are to be included in these studies.

(2) Volume has been controlled to some extent by heating the area studied through the photo-electric cell and by bringing the light and cell outlets snugly against the skin.

(3) As a guide for the surgeon during anesthesia, low oxygen saturation of the arterial blood and increased volume in the capillary bed are equally significant danger signals; hence if light absorption increases sharply due to one or the other, or both, corrective measures are indicated.

(4) If the respirations are of usual rate and amplitude, oxygen should rapidly reduce the high light absorption. Lack of response to oxygen suggests a dilated capillary bed and low blood pressure.

DISCUSSION.—DR. ROY D. McCLURE (Detroit, Mich.): We are inclined to believe that not enough attention is paid to anoxia during anesthesia. In recent years, there have been reported occasional deaths on the operating table during anesthesia. Autopsies have been obtained on these patients and the typical changes of anoxia have been demonstrated. Our attention has also been drawn to several patients in whom mental and physical derangements occurred after anesthesia. It is our opinion that these changes have been produced by anoxia.

We have one patient that I should like to report: A young lady led her class in her particular section of the first year's work. She came to Detroit one morning and had a tooth extracted under nitrous oxide. On returning to her home that afternoon she noticed that her vision was blurred, but neither she nor her parents associated this change with the pulling of the tooth. Later she consulted an oculist who tested her eyes and gave her glasses. On her return to school she noticed no further change in herself, but when the next term examinations came up she made very bad marks, and before the year was out she failed in her work. On the next visit to this dentist, a year later, for another impacted molar on the opposite side, he said to her: "For heaven's sake, don't let anybody ever give you gas again because you just can't take it." It then came out that during her first anesthesia, which was a gas anesthetic, she had become blue and had to be given artificial respiration.

In discussion of this subject with different groups of doctors there are always some who have noticed changes in a patient after anesthesia. We feel that the exact nature of these changes, despite their importance, is often not recognized and that undoubtedly many more cases of slight anoxia with permanent damage occur than is commonly suspected. I do not know how we can detect this condition except, perhaps, by earlier mental tests of patients such as this particular girl had in her school, because such changes were not even recognized by her family.

We have been attempting to study this problem of anoxia by making arterial punctures and estimating the oxygen content of the blood during anesthesia. This method is cumbersome and requires too much time to be of practical value. It is obvious that a method of such blood analysis must be immediate, and the search for some such practical method is responsible for the report given here to-day by Doctor Hartman. This method with the electric eye is immediate and striking, and we hope may soon prove to be of considerable practical importance.



## MEMOIRS

### GEORGE EMERSON BREWER

1861-1939

GEORGE BREWER'S first appearance before the American Surgical Association was when he was asked to take part in a symposium on gallbladder disease, in 1899. His paper was on the "Diagnosis of the Diseases of the Gallbladder and Ducts." The other contributors were Hans Kerr, of Halberstadt, Halsted and W. J. Mayo. The following year he was elected to membership and attended all the meetings of the Association until his retirement, in 1927, except for the years of his overseas service. During this long membership he took an active part in the proceedings and was elected president in 1920.

He was born at Westfield, N. Y., July 28, 1861, the son of Francis B. Brewer and Susan H. Rood. On June 29, 1893, he married Effie Leighton Brown, at Chester, Pa., there being two children, Leighton and George Emerson, Jr.

In his later years as teacher, as diagnostician, and in his care of his patients he showed the effects of his broad early training. While at Hamilton College, where he received the degrees of A. B., in 1881, and A. M., in 1884, he was the college organist. His first two years of medical study were spent at the University of Buffalo. During this period he lived with Dr. Julius F. Minor, Professor of Surgery, and assisted him with his operations and in his office. During these summers, he acted as apothecary at the State Insane Asylum. He entered the third-year class at Harvard University, and received his M.D. degree in 1884. Before graduation, he won first place in the intern examinations for the Boston City Hospital, where he served with Drs. Robert Lovett, John Munro and Leonard Wood. After a residency in obstetrics and gynecology at Columbia Hospital for Women, in Washington, D. C., in 1886, he went to Baltimore as "fellow by courtesy" at Johns Hopkins University, under Dr. William H. Welch. He also held a position at this time as Resident Superintendent of the Baltimore City Insane Hospital.

In 1887, he came to New York and started the general practice of medicine, working in the Out-Patient departments of Roosevelt, Bellevue and Chambers Street Hospitals. The following year, he became the assistant of Dr. Henry Holbrook Curtis, an eminent nose and throat specialist, an association that lasted five years. During these summers, he carried on an active general practice at Block Island.

His first appointment to the College of Physicians and Surgeons, Columbia University, was that of assistant in Genito-Urinary Surgery to Dr. Fessenden Nott Otis. In 1892, he became assistant demonstrator of anatomy, and during that summer studied in Edinburgh under Sir William Turner and Doctor

Hepburn. He was appointed attending surgeon at the City Hospital in 1899. It was here that he began his studies in operating room technic, which were of great influence in that important period of surgery. Two years later, he was



GEORGE EMERSON BREWER

made junior surgeon at Roosevelt Hospital and the College, with Dr. Joseph A. Blake, and founded, with him, the research laboratory of Surgical Pathology at the College. In 1913, he resigned from Roosevelt Hospital and became Surgical Director of the Presbyterian Hospital.

He was one of the original members of the Society of Clinical Surgery and its first president. He was also a member of the American Association of Genito-Urinary Surgeons, the New York Academy of Medicine, the New York Surgical Society, the Société Internationale de la Chirurgie, and the Société Internationale d'Urologie. In 1913, he was President of the Clinical Congress of Surgeons of North America, which later became the Clinical Congress of the American College of Surgeons. He was a member of the American Medical Association, and the American Urological Association. He was consulting surgeon at the City, Roosevelt, Presbyterian, St. Mark's, St. Vincent's, Woman's and Knickerbocker Hospitals, and the Manhattan Eye and Ear Infirmary of New York City; the House of the Holy Comforter, Flushing; Muhlenberg Hospital, Plainfield; the Perth Amboy Hospital, and Christ's Hospital, Jersey City.

Doctor Brewer, in addition to many articles on anatomic and surgical conditions, especially diseases of the kidney, gallbladder and large intestine, was the author of "Textbook on Surgery" (3 editions), and "Surgical Diagnosis."

On May 15, 1917, he sailed for overseas as director of Base Hospital Unit No. 2, which took charge of No. 1 General Hospital, B. E. F., at Étretat, France. He served with an operating team at Casualty Clearing Station No. 4 in the Passchendaele campaign in the summer of 1917. In February, 1918, he was made Consulting Surgeon to the 42nd Division, A. E. F., and later, chief consultant in Surgery to the First Corps and still later to the First Army, serving in the area of the advance in the Chateau Thierry, St. Mihiel and Argonne campaigns. He was later made Officier de l'Ordre de la Couronne (Belgium).

In 1916, Hamilton College conferred upon him the degree of LL.D., and, in 1929, he received from Columbia University the degree of Sc.D. (hon.). In 1920, he was made an honorary fellow of the Royal College of Surgeons of Ireland.

In 1928, Doctor Brewer retired from the practice of surgery, and immediately went to France to renew his interest and study of anthropology. Soon after his return he was made Research Associate of Somatic Anthropology at the American Museum of Natural History.

Early in 1937, it became evident that he had a neoplasm of the bladder. Although this was held in check by radiation for almost two years, in December, 1939, it became rapidly worse and he died quietly on Christmas Eve, 1939.

WILLIAM DARRACH.

ALEXIUS McGLANNAN, A.M., M.D., LL.D.

1872-1940

DR. ALEXIUS McGLANNAN died at his home, 115 West Franklin Street, Baltimore, Sunday, February 25, 1940, after an illness of considerable duration. Doctor McGlannan was born in Baltimore, July 24, 1872, his parents



ALEXIUS McGLANNAN, M.D.

being Alexius W. McGlannan and Agnes Veronica Gallagher McGlannan. His preliminary education was received at Calvert Hall College, and he was graduated in medicine by the College of Physicians and Surgeons, now combined with the University of Maryland, in 1895, and soon became actively engaged in teaching in this institution.

At first he seemed inclined to medical subjects, with a particular interest in chemistry, but soon decided that surgery was to be his life's work and became connected with this department, quickly working his way upward. He had the conception, more universally stressed by many later, that the study of pathology is an important foundation to good surgery, and became rather closely associated with the late Dr. Joseph C. Bloodgood in his laboratory at the Johns Hopkins Hospital, and in his clinical work at St. Agnes Hospital. His emphasis on pathology in his operative clinics, ward classes and lectures was a distinguishing characteristic of his teaching.

Doctor McGlannan's great energy, his fidelity to his work, and an unusual memory, soon bore fruit in rapid advancement in his chosen specialty. By 1915, he had become Professor of Clinical Surgery and Surgical Pathology at the College of Physicians and Surgeons. In 1930, he was made Professor of Surgery at the School of Medicine, University of Maryland, the two schools having been combined. In 1926, he was made Chief Surgeon of Mercy Hospital, Baltimore, where most of his work had been done and where he advanced step by step.

These positions entailed so much work that he eventually declined to operate except in the hospital with which he was so closely allied and for which he did so much, though he was on the Staffs of several others. In 1933, his health became impaired and necessitated curtailment of his activities, but by this time, he had accomplished a prodigious amount of work and achieved many honors. In addition to the positions already mentioned, he had been honored by numerous offices in the Medical and Chirurgical Faculty of Maryland, doing almost unlimited work on its committees, and was elected its President in 1929.

In addition to the City and State Societies and the American Medical Association, he was a member of the American Surgical Association, Southern Surgical Association, American College of Surgeons and American Gastro-Enterologic Association, and contributed many papers to these societies and to medical journals. In fact, it might be said that during his active years, besides the operative work of a large clinic, much teaching and caring for a large private practice, he wrote a great deal. One sees his articles in *Systems of Surgery and Medicine*, and his name in many bibliographies. The number of his published articles totals nearly 100.

Apparently, Doctor McGlannan felt that "opportunity is kind but only to the industrious." He had none of the usual avocations, such as golf, hunting or fishing, though he did some boating on Saranac Lake where he spent the summers at his elaborate camp. He did not drink, smoke or play cards. General reading and music were his recreations. He never ceased studying, even when he no longer operated.

Doctor McGlannan's reading was of a wide range with Surgery as the central theme, but he seemed to gather information easily and retain it permanently about all manner of subjects. This naturally added to his value



as a consultant in diagnosis and treatment, and enabled him to, surpassingly well, avoid being the type of surgeon who is only an operator.

Doctor McGlannan's first wife, who was Miss Anna Maria Crean, died in 1902. They had one son, Alexius McGlannan III. In 1907, he married Dr. Sallie Porter Law, who was graduated in medicine at the Johns Hopkins Medical School that year but never practiced. Mrs. McGlannan is a gifted artist and illustrated Doctor McGlannan's surgical papers. There were no children by this marriage. He is survived by Mrs. McGlannan, his son by his first marriage, and nieces and nephews.

One could pay tribute to Doctor McGlannan's ability, his industry, his accomplishments in surgery, or his devotion to the Roman Catholic religion and his exemplary life, but to many colleagues, house officers, students, and countless patients, his outstanding characteristics were friendliness and kindness and, above all, charitableness. He lent strength to the quotation, "Charity suffereth long and is kind; charity envieth not; charity vaunteth not itself, is not puffed up."

WALTER D. WISE.

#### GOVERNMENT TO NEED TEMPORARY AND PART-TIME CIVILIAN MEDICAL OFFICERS

THE expansion of the army creates a need for about 600 civilian medical officers in various grades for temporary and part-time service. The duties of full-time officers will be to act as doctors of medicine in active practice in hospitals, in dispensaries, and in the field. The duty of part-time officers will be to report for sick call at a fixed hour each day and to be subject to emergency call at all times.

The Civil Service Commission in making this announcement calls particular attention to the fact that part-time officers will be able to continue their regular practice. In order that this may be done, appointments to the part-time positions will be made of medical officers in the vicinity of the place of duty.

Information concerning these positions may be obtained from the Secretary of the Board of U. S. Civil Service Examiners at any first- or second-class post office, or from the United States Civil Service Commission, Washington, D. C. Physicians are urged to apply at once. This work is of the greatest importance to the success of the National Defense program.

AUGUST 31, 1940.

#### EDITORIAL ADDRESS

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St. Louis, Mo., May 2, 1940

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